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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2000). Trends Cardiovasc. Med., 10(6):229-37)

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis; dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

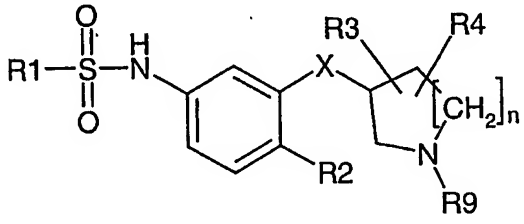
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

R_1 is phenyl, thienyl, furanyl, pyrroyl, pyridinyl, oxazoyl, indoyl, triazinyl, imidazoyl, pyrimidinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, or pyrazinyl substituted or

unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, OH, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-CF_3, $O(CH_2)_qY$, NR_5R_6, $N(C_{1-6}$ alkyl)$CO(C_{1-6}$ alkyl), COR_{10}, $CONR_7R_8$, $S(O)_pC_{1-6}$ alkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$NHCOR_{11}$, or $CH(OH)C_{1-6}$ alkyl;

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3 and R_4 are independently hydrogen, C $_{1-6}$ alkyl, benzyl, $-C(R_{14})_2-OR_{12}$, $-COOR_{13}$, $-CONR_{12}$, $-C(R_{14})_2-N(R_{12})_2$;

R_5 and R_6, are independently hydrogen or C_{1-6} alkyl, or taken together form a 5-7-member saturated heterocycle optionally containing an additional heteroatom selected from N, O or S and further substituted by hydrogen, C_{1-6} alkyl, benzyl or OH;

R_7 and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl; or taken together form a 5-7-member saturated heterocycle optionally containing an additional heteroatom selected from N, O or S and further substituted by hydrogen, C_{1-6} alkyl, benzyl or OH;

R_9 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_mR_{15}$;

R_{10} is hydrogen or C_{1-6} alkyl;

R_{11} is C_{1-6} alkyl or benzyl

R_{12} is hydrogen or C $_{1-6}$ alkyl;

R_{13} is C $_{1-6}$ alkyl;

R_{14} is hydrogen or C_{1-3}alkyl;

R_{15} is phenyl, OH, or $-(C=O)C_{1-3}$alkyl;

X is O, S, or CH_2;

Y is a 5-7 member saturated heterocycle containin up to 2 heteroatoms selected from N, O or S, optionally substituted by hydrogen, C $_{1-6}$ alkyl or benzyl;

n is 0, 1 or 2;

m is 1 or 2 ;

p is 0, 1 or 2;

q is 0 or 1;

provided that when R_{14} is OH, m must be 2;

further provided that the compound of Formula (I) is not:

3,5-dichloro-4-hydroxy-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

5-[cyclohexyl(hydroxy)methyl]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-(cyclohexylmethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-fluorobenzenesulfonamide; ;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

R_1 is preferably phenyl, thienyl, furanyl, pyrroyl, pyridinyl, oxazoyl, imidazoyl, pyrimidinyl, pyrazoyl, or thiazoylsubstituted or unsubstituted by one, two, or three, of any of the following: Cl, Br, F. CF_3, OH, NO_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, $O(CH_2)_qY$, NR_5R_6, COR_{10}, $CONR_7R_8$, $S(O)_pC_{1-3}$ alkyl, CO_2H, or $CH(OH)C_{1-4}$ alkyl.

R_2 is preferably hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl.

R_3 and R_4 are preferably hydrogen, C_{1-3} alkyl, $-C(R_{14})_2-OR_{12}$.

R_7 and R_8 are preferably hydrogen, C_{1-3} alkyl, or taken together form morpholine or piperidine.

R_5 and R_6 are preferably hydrogen or C_{1-3} alkyl, or taken together form morpholine, piperidine, or pyrrolidine.

R_9 is preferably hydrogen, C_{1-3} alkyl.

R_{10} is preferably hydrogen, C_{1-3} alkyl.

R_{12} is preferably hydrogen or C_{1-3} alkyl.

R_{14} is preferably independently hydrogen or methyl.

X is preferably O.

Y is preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperadinyl, azetidinyl all of which may be optionaly substituted by C_{1-3} alkyl

n is preferably 1.

p is 0, 1 or 2

q is 0 or 1

Preferred compounds are:

N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

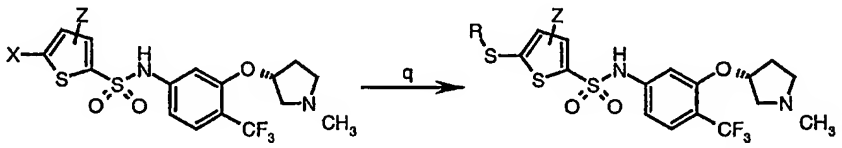
N-[3-(2(R)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4,5-dimethoxybenzenesulfonamide;

N-[3-((R)-pyrrolidin-3-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide.

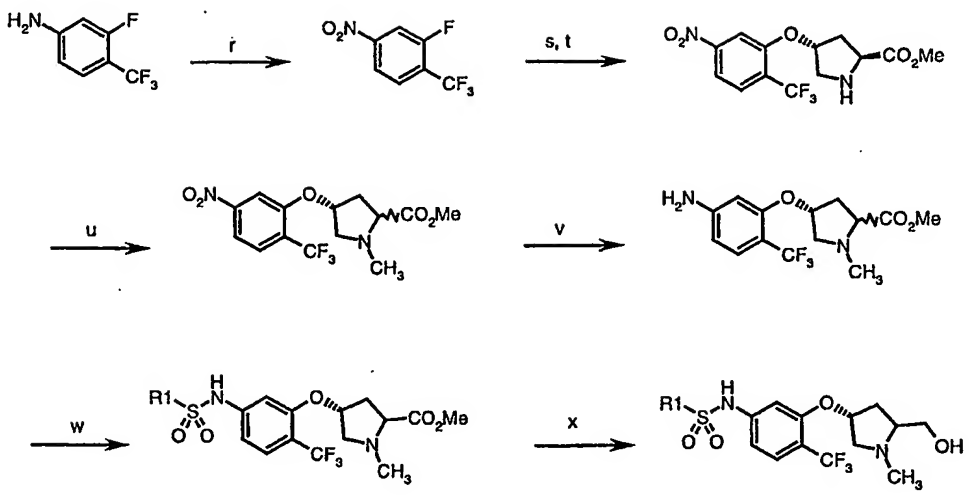
Compounds of Formula (I) may be prepared as outlined in Scheme 1.

Scheme 1



q) mercaptan, NaOH solution, DMF, heat. (X is Cl or Br, Z from the list of substuients on R1)

Scheme 2

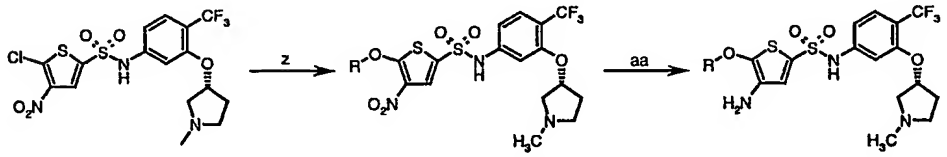


r) hydrogen peroxide, trifluoroacetic acid; s) sodium hydride, 2(S)3(R)-N-Boc-hydroxyproline methyl ester; t) 4M HCl, dioxane; u) formaldehyde, sodium triacetoxyborohydride; v) hydrogen, palladium on carbon; w) $R1SO_2Cl$, pyridine; x) lithium aluminum hydride or lithium borohydride

Scheme 3

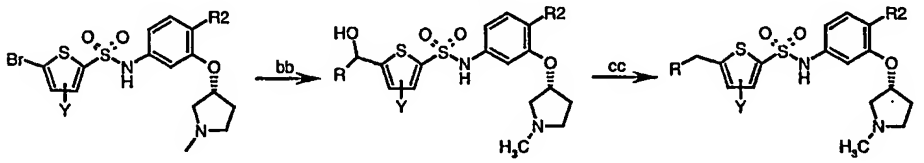
y) RCHO, sodium cyanoborohydride or RBr, potassium iodide, potassium carbonate.

Scheme 4



z) cesium carbonate, DMF, ROH. aa) iron powder, HOAc. (R is alkyl)

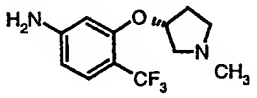
Scheme 5



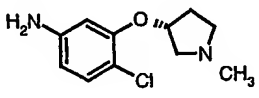
bb) *n*-BuLi, RCHO, THF, –78°C. cc) Triethylsilane, TFA, CH_2Cl_2, rt. (Y is halogen or hydrogen)

Sulfonyl chlorides, when not commercially available, can be prepared by methods known in the art: Shahripour, A.B. et al. *Bioorg. Med. Chem.* **2002**, *10*, 31; Cross, P.E. et al. *J. Med. Chem.* **1978**, *21*, 845; Huntress et al *J. Amer. Chem. Soc.* **1941**, *63*, 3446; Hashimoto, H. et al *J. Med. Chem.* **2002**, *45*, 1511.

Anilines **A** and **B** have been previously described: WO 2002089792 A1 incorporated by reference herein.



Aniline **A**



Anline **B**

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any

pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal

disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 1 nM – 10000 nM. (Example 6 = 21nm)

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

3-Fluoro-4-trifluoromethylnitrobenzene:

3-Fluoro-4-trifluoromethylaniline (15.10 g, 85.4 mmole) was dissolved on CF_3CO_2H (85 ml). H_2O_2 (50% in H_2O, 42 ml 1.46mole, 7 eq) was added dropwise over 35 min. The mixture was stirred and heated at 45°C for 2 hr and 65°C for 40 min before being cooled to rt and poured into ice/water (600 ml). The mixture was stirred overnight. Ether (250 ml) was added and the organic layer was separated. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, twice with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow oil (17.10 g, 96%).

Example 2

3-[2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl nitrobenzene:

A solution of the compound of Example 1 (3.14 g, 15 mmole) and 2(S)3(R)-N-*tert*-butoxycarbonylhydroxyproline methyl ester (3.68g, 15 mmole) in dry THF (75 ml) was cooled to 0°C and then NaH (60% in mineral oil, 1.20 g, 30 mmole) was added protionwise over 5

min. The mixture was stirred and allowed to warm to rt. Once at rt, the mixture was stirred an additional 2 hr. The solvent was removed under reduced pressure and then the residue was dissolved in MeOH (75 ml). 4M HCl in dioxane (20 ml) was added and the resultant mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The aqueous layer was adjusted to pH 7 using aqueous Na_2CO_3 and then was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated to give the title compound as a yellow oil (2.50 g, 50%). MS (ES) m/e 335.2 $[M+H]^+$.

Example 3

3-[1-methyl-2(R/S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl nitrobenzene:

The compound of Example 2 (3.20 g, 9.6 mmole) and formaldehyde (37% wt. in water, 0.94 g, 11.5 mmole, 1.2 eq) was dissolved in CH_2Cl_2 (70 ml). $Na(OAc)_3BH$ (3.01 g, 14.4 mmole, 1.5 eq) was added and the resultant mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was purified by column chromatography (150 g silica gel 60, 230-400 mesh, CH_2Cl_2 then 1% MeOH in CH_2Cl_2 then 2% MeOH in CH_2Cl_2 as eluent) to give 2.80 g (73%) of a mixture of diastereomers as a yellow oil. MS (ES) m/e 349.0 $[M+H]^+$.

Example 4

3-[1-Methyl-2(R/S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl aniline:

Pd-C (10 %, 0.9g) added to a solution the compound of Example 3 (1.96 g, 5.6 mmol) and MeOH (50 mL). The resulting mixture was shaken under a H_2 atmosphere (50 psi) for 3h. The mixture was then filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give 1.8 g (100%) of the title compound as a tan oil. MS (ES) m/e 319.2 $[M+H]^+$.

Example 5

N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:

Pyridine (0.35 g, 4.4 mmol), followed by the compound of Example 4 (1.41 g, 4.4 mmol) was added to a solution of 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (1.40 g, 4.4

mmol) and acetonitrile (10 mL). The resultant mixture was stirred at rt overnight. The mixture was concentrated and purified by silica gel chromatography COMBIFLASH CONDITIONS to give 1.24 g (47%) of N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide. MS (ES^+) m/e 597.2 $[M+H]^+$. and XXX g (XX%) of N-[3-(1-methyl-2(R)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide. MS (ES) m/e 597.2 $[M+H]^+$.

Example 6

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:

$LiBH_4$ (0.24 g, 1.1 mmol) was added to a solution of the compound of Example 5 (0.6 g, 1.0 mmol) and THF (10 mL) and the resultant mixture was stirred at rt overnight. The mixture was then diluted with MeOH and concentrated. The residue was dissolved in MeOH (10 mL), 2N HCl was added (10 mL) and the solution allowed to stand overnight. The solution was then concentrated in vacuo and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 100 mg (17%) of the title compound as a white solid. MS (ES) m/e 569.2 $[M+H]^+$.

Example 7

N-[3-(2(R)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:

$LiBH_4$ (24 mg, 0.11 mmol) was added to a solution of the compound of Example 6 (60 mg, 0.1 mmol) and THF (1 mL). The resultant mixture was stirred at rt overnight. Satd NH_4Cl was added and the mixture extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and 2N HCl (2 mL) and stirred overnight. The mixture was concentrated under reduced pressure and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 4.4 mg (8%) of the title compound as a tan oil. MS (ES) m/e 569.2 $[M+H]^+$.

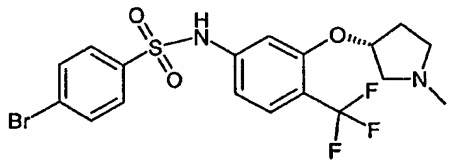
Example 8

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-3,4-dimethoxybenzenesulfonamide:

A solution of the compound of Example 6 (0.30 g, 0.50 mmol) and THF (2mL) was added dropwise to a solution of 1 M $LiAlH_4$ in ether (1.0 mL, 1.0 mmol). The mixture was stirred at rt for 20 min and then another portion of $LiAlH_4$ (2.0 mL, 2.0 mmol) was added. The mixture was stirred an additional 45 min before being quenched with water (0.22 mL) and NaF (0.38 g, 9.1 mmol). The mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo. The residue was purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 35 mg (14%) of the title compound as a tan solid. MS (ES) m/e 491.2 $[M+H]^+$.

Example 9

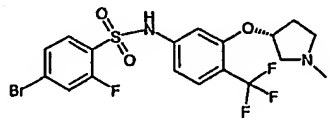
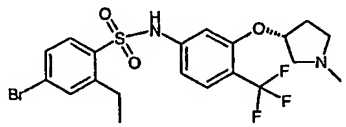
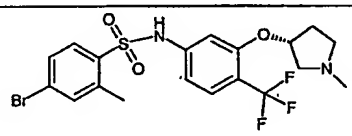
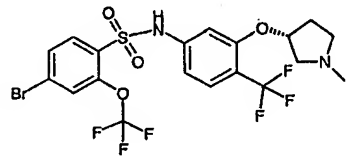
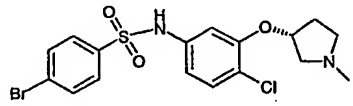
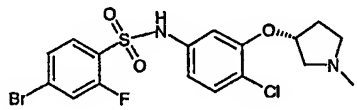
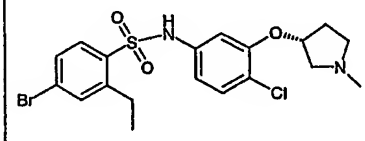
4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl] benzenesulfonamide:

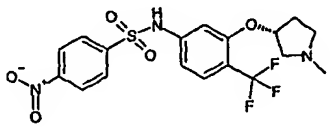
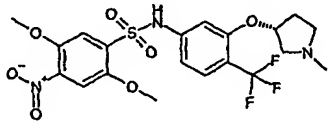
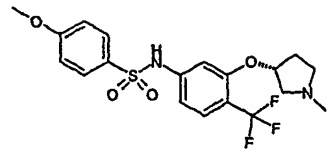
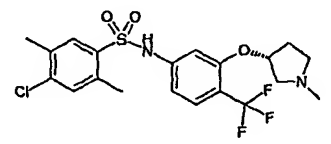
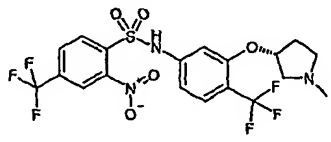
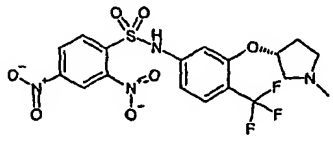
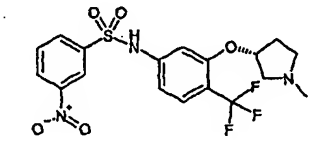
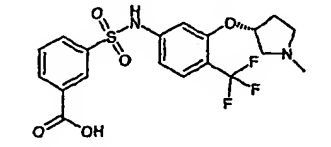


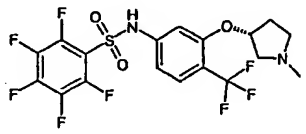
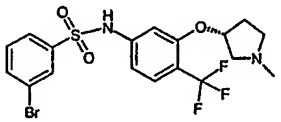
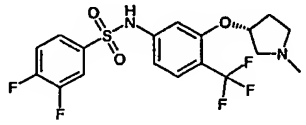
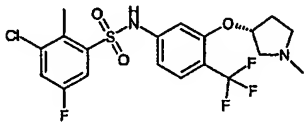
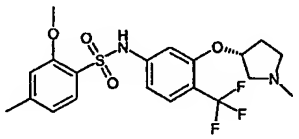
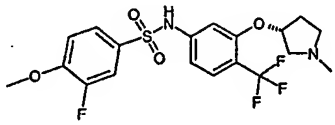
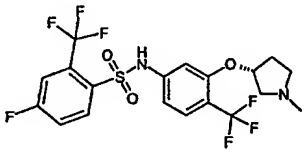
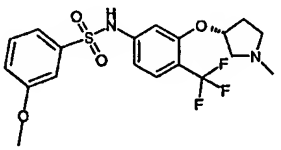
Aniline A (39 mg, 0.15 mmol) was dissolved in 1 mL of methylene chloride and treated with 4-bromobenzenesulfonyl chloride (46.0 mg, 0.18 mmol) and pyridine (0.024 mL, 0.30 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 1 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:5 to 95% during 12 min, UV detection at 214 nm) to give 47.7 mg (66%) of the title compound as a pale yellow oil. MS (ES) m/e 479 [M+H]+

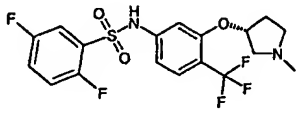
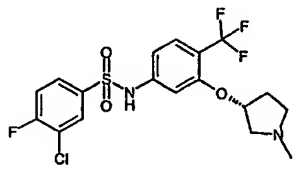
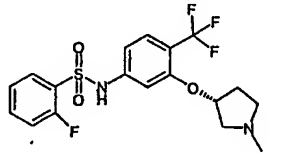
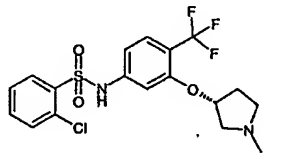
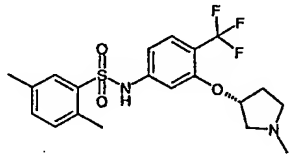
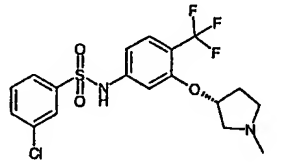
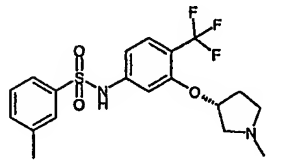
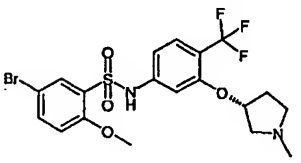
Examples 10-137

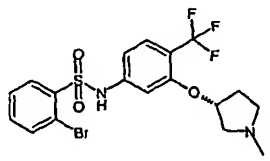
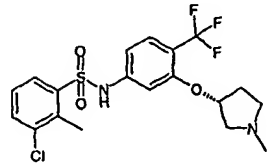
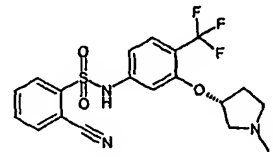
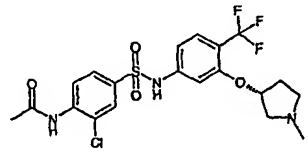
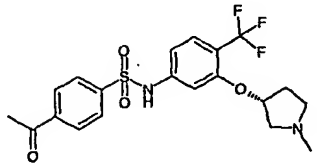
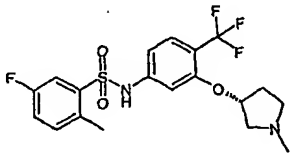
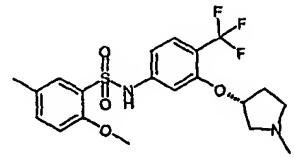
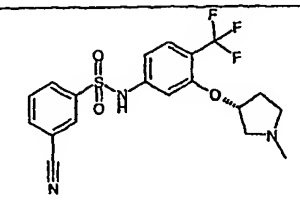
The following examples were prepared according to the representative procedure in **Example 1**? using the appropriate sulfonyl chlorides as starting material, in some cases using acetonitrile rather than methylene chloride as the solvent, and in some cases also substituting Aniline A for Aniline B.

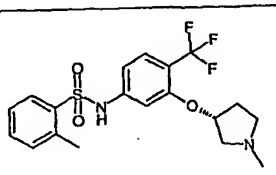
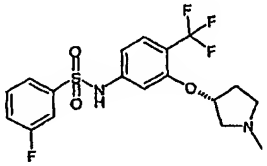
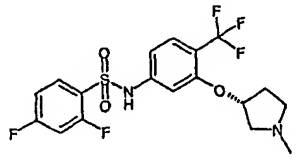
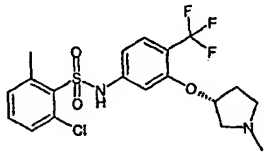
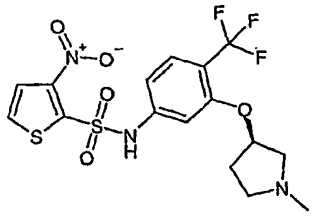
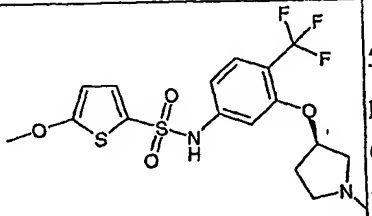
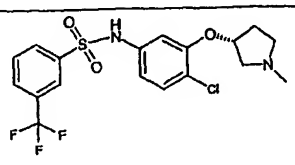
#	structure	name	m/z
10		4-bromo-2-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	497
11		4-bromo-2-ethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	507
12		4-bromo-2-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	495
13		4-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-[(trifluoromethyl)oxy]benzenesulfonamide	563
14		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	447
15		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-fluorobenzenesulfonamide	463
16		4-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-ethylbenzenesulfonamide	473

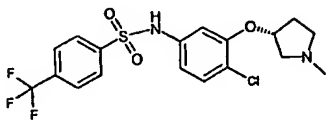
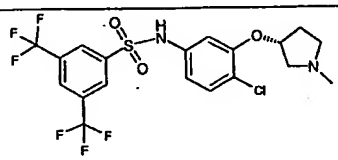
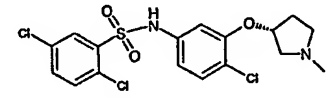
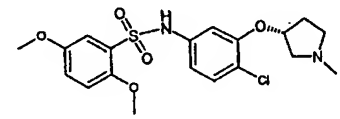
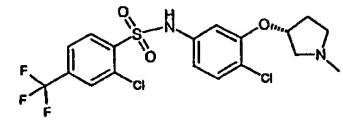
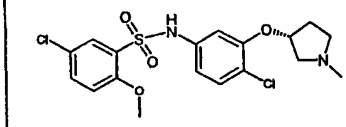
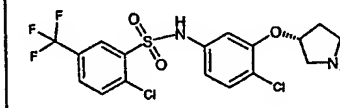
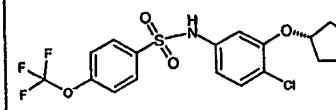
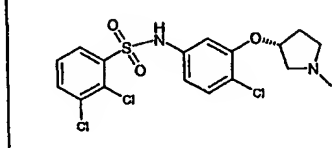
17		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitrobenzenesulfonamide	446
18		2,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitrobenzenesulfonamide	506
19		4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	431
20		4-chloro-2,5-dimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	463
21		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-nitro-4-(trifluoromethyl)benzenesulfonamide	514
22		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,4-dinitrobenzenesulfonamide	491
23		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-nitrobenzenesulfonamide	446
24		3-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)benzoic acid	445

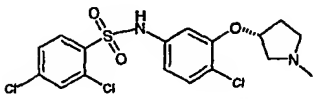
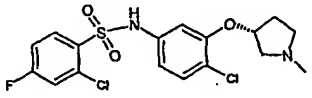
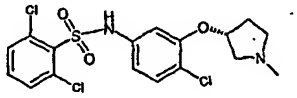
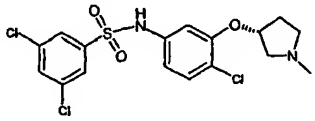
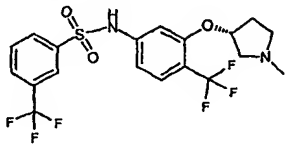
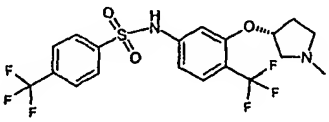
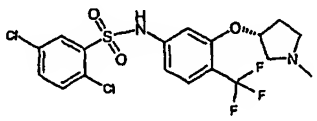
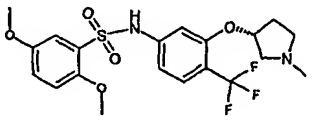
25		2,3,4,5,6-pentafluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	491
26		3-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	479
27		3,4-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	437
28		3-chloro-5-fluoro-2-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	467
29		4-methyl-2-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	445
30		3-fluoro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	449
31		4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-(trifluoromethyl)benzenesulfonamide	487
32		3-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	431

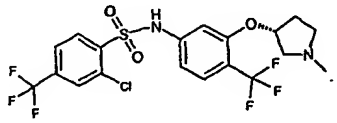
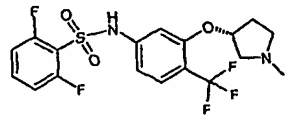
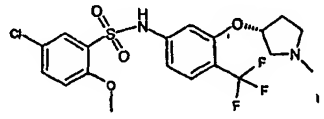
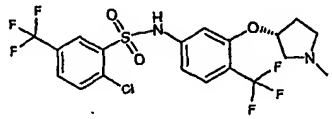
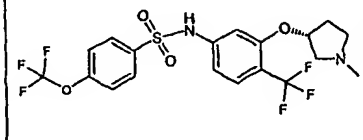
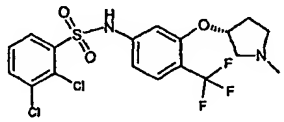
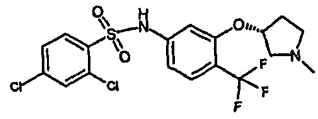
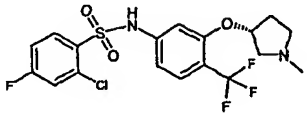
33		2,5-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	437
34		3-chloro-4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	453
35		2-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	419
36		2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	435
37		2,5-dimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	429
38		3-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	435
39		3-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	415
40		5-bromo-2-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	509

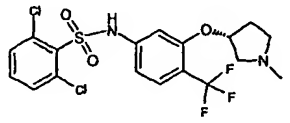
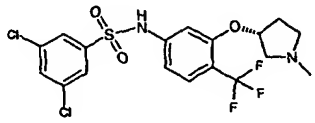
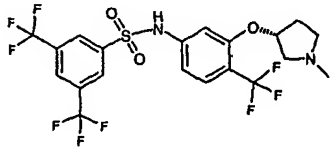
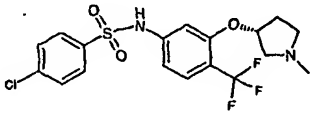
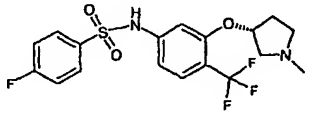
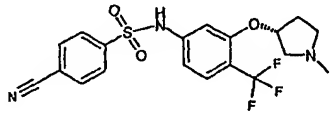
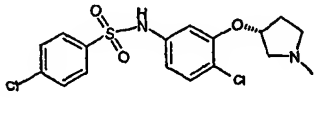
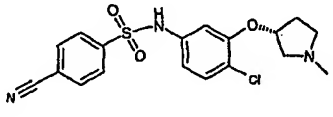
41		2-bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	479
42		3-chloro-2-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	449
43		2-cyano-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	426
44		N-[2-chloro-4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]acetamide	492
45		4-acetyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	443
46		5-fluoro-2-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	433
47		5-methyl-2-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	445
48		3-cyano-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	426

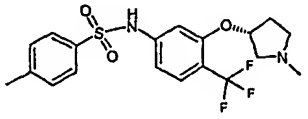
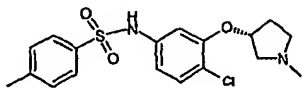
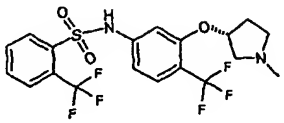
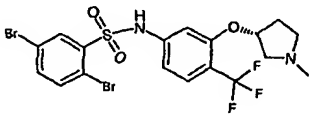
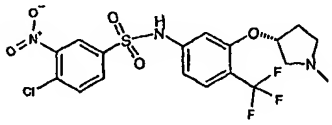
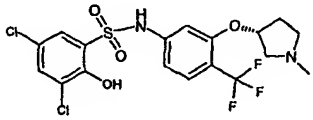
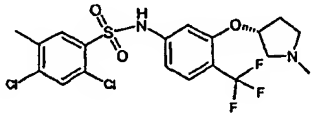
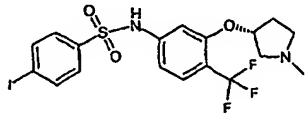
49		2-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	415
50		3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	419
51		2,4-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide ,	437
52		2-chloro-6-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	449
53		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-nitro-2-thiophenesulfonamide	452.0
54		5-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	437
55		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-(trifluoromethyl)benzenesulfonamide	435

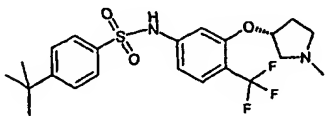
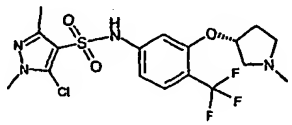
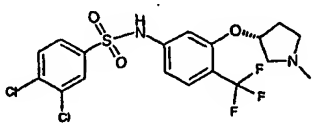
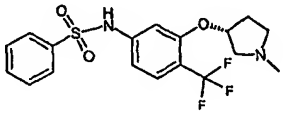
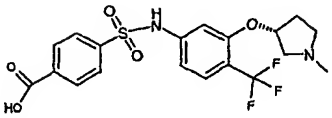
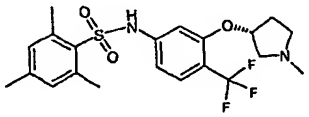
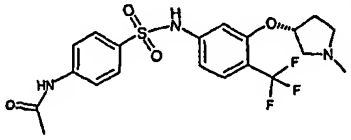
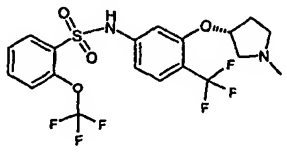
56		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(trifluoromethyl)benzenesulfonamide	435
57		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide	503
58		2,5-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	438
59		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,5-bis(methyloxy)benzenesulfonamide	427
60		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(trifluoromethyl)benzenesulfonamide	469
61		5-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-(methyloxy)benzenesulfonamide	432
62		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-(trifluoromethyl)benzenesulfonamide	469
63		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-[(trifluoromethyl)oxy]benzenesulfonamide	451
64		2,3-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	436

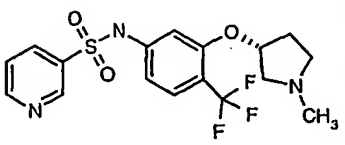
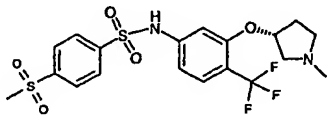
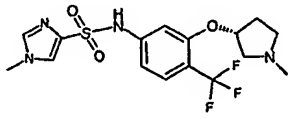
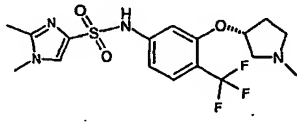
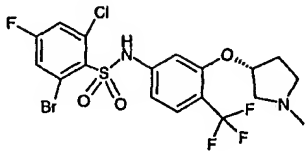
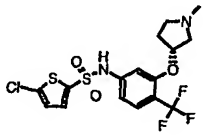
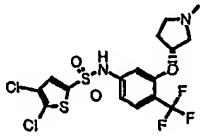
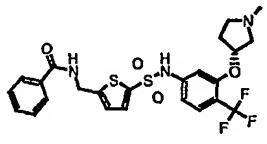
65		2,4-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	436
66		2-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-fluorobenzenesulfonamide	419
67		2,6-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	436
68		3,5-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	436
69		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide	468
70		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	468
71		2,5-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
72		2,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	460

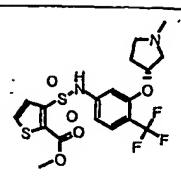
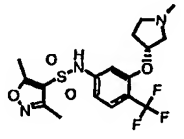
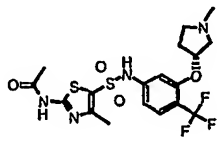
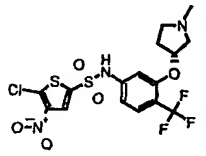
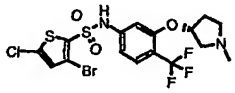
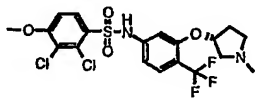
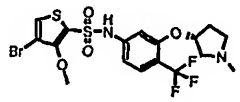
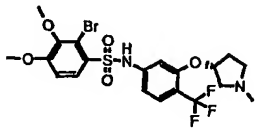
73		2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide	503
74		2,6-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	436
75		5-chloro-2-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	465
76		2-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(trifluoromethyl)benzenesulfonamide	503
77		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)oxy]benzenesulfonamide	484
78		2,3-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
79		2,4-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
80		2-chloro-4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	453

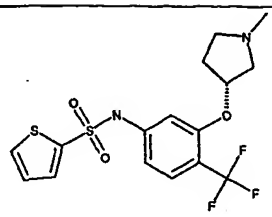
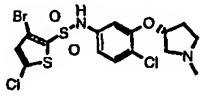
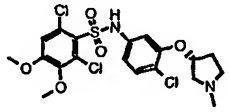
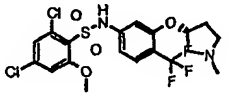
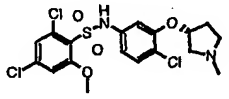
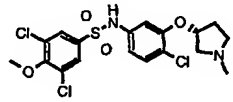
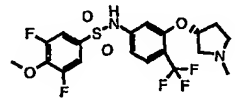
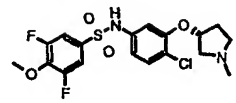
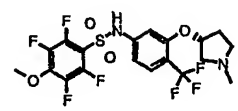
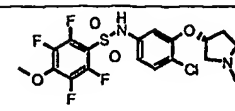
81		2,6-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
82		3,5-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
83		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3,5-bis(trifluoromethyl)benzenesulfonamide	536
84		4-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	435
85		4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	418
86		4-cyano-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	426
87		4-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)benzenesulfonamide	401
88		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-cyanobenzenesulfonamide	392

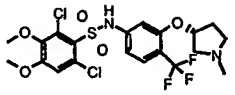
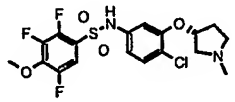
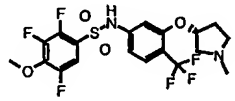
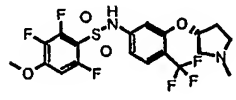
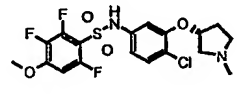
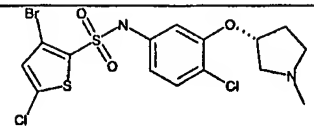
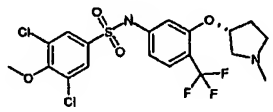
89		4-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	415
90		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-methylbenzenesulfonamide	381
91		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-(trifluoromethyl)benzenesulfonamide	469
92		2,5-dibromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	558
93		4-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-nitrobenzenesulfonamide	480
94		3,5-dichloro-2-hydroxy-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	485
95		2,4-dichloro-5-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	483
96		4-iodo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	526

97		4-(1,1-dimethylethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	457
98		5-chloro-1,3-dimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-sulfonamide	453
99		3,4-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	469
100		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	401
101		4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)benzoic acid	444
102		2,4,6-trimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	443
103		N-[4-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)phenyl]acetamide	458
104		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-[(trifluoromethyl)oxy]benzenesulfonamide	485

105		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-pyridinesulfonamide	402
106		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(methylsulfonyl)benzenesulfonamide	479
107		1-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1H-imidazole-4-sulfonamide	405
108		1,2-dimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1H-imidazole-4-sulfonamide	419
109		2-bromo-6-chloro-4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	532
110		5-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	441
111		4,5-dichloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	475
112		N-{[5-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-2-thienyl]methyl}benzamide	540

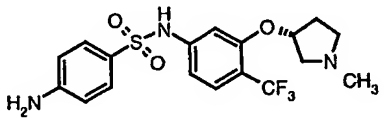
113		methyl 3-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-2-thiophenecarboxylate	465
114		3,5-dimethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-isoxazolesulfonamide	420
115		N-[4-methyl-5-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-1,3-thiazol-2-yl]acetamide	479
116		5-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	486
117		3-bromo-5-chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	519
118		2,3-dichloro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	499
119		4-bromo-3-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	515
120		2-bromo-3,4-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	538

121		N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	407
122		3-bromo-5-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-thiophenesulfonamide	485
123		2,6-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3,4-bis(methyloxy)benzenesulfonamide	495
124		2,4-dichloro-6-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	499
125		2,4-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-(methyloxy)benzenesulfonamide	465
126		3,5-dichloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(methyloxy)benzenesulfonamide	465
127		3,5-difluoro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	467
128		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3,5-difluoro-4-(methyloxy)benzenesulfonamide	433
129		2,3,5,6-tetrafluoro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	503
130		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,3,5,6-	469

		tetrafluoro-4-(methyloxy)benzenesulfonamide	
131		2,6-dichloro-3,4-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	529
132		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,3,5-trifluoro-4-(methyloxy)benzenesulfonamide	451
133		2,3,5-trifluoro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	485
134		2,3,6-trifluoro-4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide	485
135		N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,3,6-trifluoro-4-(methyloxy)benzenesulfonamide	451
136		3-Bromo-5-chloro-thiophene-2-sulfonic acid [4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-amide	485
137		3,5-Dichloro-N-(4-trifluoromethyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4-methoxy-benzenesulfonamide	499

Example 138

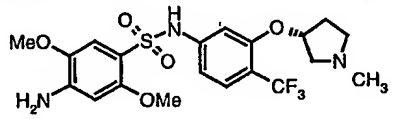
4-amino-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl] benzenesulfonamide:



N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitrobenzenesulfonamide (216 mg, 0.487 mmol) was dissolved in 5 mL of methanol and the solution was degassed with argon. Then, the solution was treated with 10 % Pd on Carbon (21.6 mg) and the flask was flushed with hydrogen gas. The reaction was stirred under an atmosphere of hydrogen for 18 hours, and then the mixture was filtered through Celite and concentrated to dryness under vacuum to give 188.9 mg (93 %) of the title compound as a white powder. MS (ES) m/e 417 $[M+H]^+$

Example 139

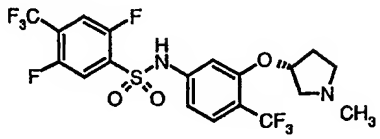
4-amino-2,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide



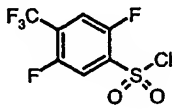
2,5-bis(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitrobenzenesulfonamide (54.6 mg, 0.108mmol) was dissolved in 5 mL of methanol and the solution was degassed with argon. Then, the solution was treated with 10 % Pd on Carbon (5.5 mg) and the flask was flushed with hydrogen gas. The reaction was stirred under an atmosphere of hydrogen for 18 hours, and then the mixture was filtered through Celite and concentrated to dryness under vacuum to give 44.5 mg (87 %) of the title compound as a colorless film. MS (ES) m/e 476 $[M+H]^+$

Example 140

2,5-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide

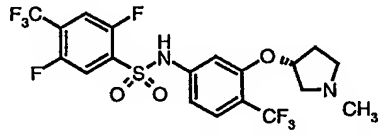


a) 2,5-difluoro-4-trifluoromethyl-benzenesulfonyl chloride



2,5-difluoro-4-trifluoromethyl-aniline (500 mg, 2.54 mmol) was dissolved in 1 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 0.498 mL, 3.81 mmol) and *tert*-butyl nitrite (0.453 mL, 3.81 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (377 mg, 3.81 mmol) in 3 mL of glacial acetic acid at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 35 mL of an ice/water slurry, causing the product to precipitate as 401.1 mg (56 %) of an orange solid which was used directly in the next step without further purification.

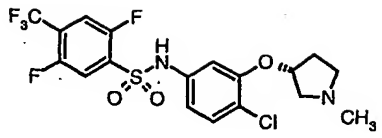
b) 2,5-difluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



Aniline A (186 mg, 0.715 mmol) was dissolved in 2 mL of methylene chloride and treated with the product of Example 134a [2,5-difluoro-4-trifluoromethyl-benzenesulfonyl chloride] (200 mg, 0.715 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:5 to 95% during 12 min, UV detection at 214 nm) to give 10.9 mg (3%) of the title compound as a yellow solid. MS (ES) m/e 505 $[M+H]^+$

Example 141

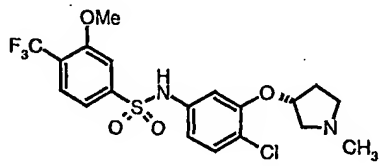
N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,5-difluoro-4-(trifluoromethyl)benzenesulfonamide



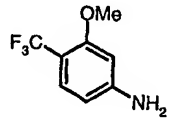
Aniline B (162 mg, 0.715 mmol) was dissolved in 2 mL of methylene chloride and treated with the product of Example 134a [2,5-difluoro-4-trifluoromethyl-benzenesulfonyl chloride] (200 mg, 0.715 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A:5 to 95% during 12 min, UV detection at 214 nm) to give 72.4 mg (22%) of the title compound as a yellow solid. MS (ES) m/e 471 $[M+H]^+$

Example 142

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-(methyloxy)-4-(trifluoromethyl)benzenesulfonamide

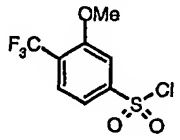


a) 3-(methyloxy)-4-(trifluoromethyl)aniline



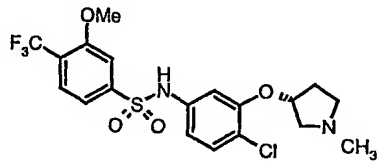
2-(methyloxy)-4-nitro-1-(trifluoromethyl)benzene (5.00 g, 22.6 mmol) was dissolved in 200 mL of methanol and the solution was degassed with argon. Then, the solution was treated with 10 % Pd on Carbon (800 mg) and the flask was flushed with hydrogen gas. The reaction was stirred under an atmosphere of hydrogen for 18 hours, and then the mixture was filtered through Celite and concentrated to dryness and under vacuum and crystallized to give 4.20 g (97 %) of the product as a light orange crystalline solid. MS (ES) m/e 192 $[M+H]^+$

b) 3-(methyloxy)-4-(trifluoromethyl)benzenesulfonyl chloride



The product of Example 136a [3-(methyloxy)-4-(trifluoromethyl)aniline] (500 mg, 2.62 mmol) was dissolved in 1 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 0.512 mL, 3.92 mmol) and *tert*-butyl nitrite (0.466 mL, 3.92 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (388 mg, 3.92 mmol) in 3 mL of glacial acetic acid at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 35 mL of an ice/water slurry, causing the product to precipitate as 588.6 mg (82 %) of a water-insoluble brown oil which was separated from the aqueous layer via pipette, dissolved in diethyl ether, dried over anhydrous sodium sulfate, filtered, and concentrated to a crude oil which was used directly in the next step without further purification.

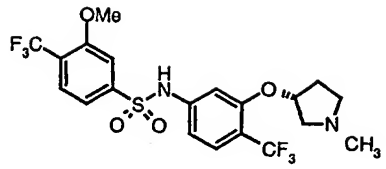
c) N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-(methyloxy)-4-(trifluoromethyl)benzenesulfonamide



Aniline **B** (243 mg, 1.07 mmol) was dissolved in 2 mL of acetonitrile and treated with the product of Example 136b [3-(methyloxy)-4-(trifluoromethyl) benzenesulfonyl chloride] (294.3 mg, 1.07 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 12 min, UV detection at 214 nm) to give 207.2 mg (42%) of the title compound as a tan solid. MS (ES) m/e 465 $[M+H]^+$

Example 143

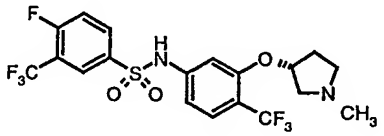
3-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



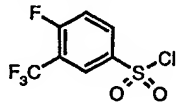
Aniline A (278 mg, 1.07 mmol) was dissolved in 2 mL of acetonitrile and treated with the product of Example 136b [3-(methyloxy)-4-(trifluoromethyl) benzenesulfonyl chloride] (294.3 mg, 1.07 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 12 min, UV detection at 214 nm) to give 110.6 mg (21%) of the title compound as a tan solid. MS (ES) m/e 499 $[M+H]^+$

Example 144

4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide



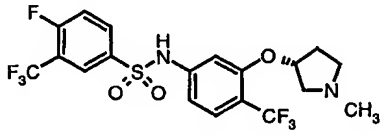
a) 4-fluoro-3-(trifluoromethyl)benzenesulfonyl chloride



4-fluoro-3-(trifluoromethyl)aniline (1.40 g, 7.82 mmol) was dissolved in 3 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 1.53 mL, 11.7 mmol) and *tert*-butyl nitrite (1.39 mL, 11.7 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (1.16 g, 11.7 mmol) in 9 mL of glacial acetic acid at 0°C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 200 mL of an ice/water slurry. The aqueous suspension was extracted with ether (2 x 200 mL) and the combined organic layers were washed twice with water (400 mL), washed once with saturated NaCl (400 mL), dried

over sodium sulfate, filtered, and concentrated to 1.9 g (93%) of an orange oil which was used directly in the next step without further purification.

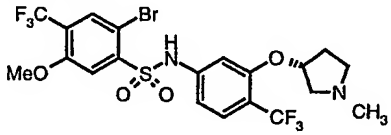
b) 4-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide



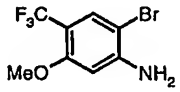
Aniline A (1.00 g, 3.84 mmol) was dissolved in 30 mL of acetonitrile and treated with the product of Example 138a [4-fluoro-3-(trifluoromethyl) benzenesulfonyl chloride] (1.9 g, 7.23 mmol) and pyridine (1.24 mL, 15.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 5 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 50 mm, 50 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 1.04 g (56%) of the title compound as a yellow foam. MS (ES) m/e 487 $[M+H]^+$

Example 145

2-bromo-5-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide



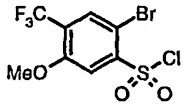
a) 2-bromo-5-(methyloxy)-4-(trifluoromethyl)aniline



The product of Example 142a [3-(methyloxy)-4-(trifluoromethyl)aniline] (2.00 g, 10.5 mmol) was dissolved in 22 mL of anhydrous dioxane and 4.5 mL of acetic acid and cooled to 0 °C. Then, a solution of bromine (0.592 mL, 11.6 mmol) in 20 mL of anhydrous dioxane was added dropwise over a 10 minute period. The reaction was allowed to warm to room temperature and stir for one hour, after which time it was poured into 100 mL of 1M NaOH and 100 mL of 2M sodium carbonate. The aqueous suspension was extracted with methylene chloride (3 x 100 mL) and the combined organic layers were washed with 0.5 M sodium carbonate (100 mL),

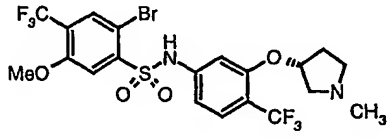
washed with saturated sodium chloride (100 mL), dried over sodium sulfate, filtered, and concentrated to 2.69 g (95 %) of an orange oil which crystallized upon standing. This material was used directly in the next step without further purification.

b) 2-bromo-5-(methyloxy)-4-(trifluoromethyl)benzenesulfonyl chloride



The product of Example 145a [2-bromo-5-(methyloxy)-4-(trifluoromethyl) aniline] (1.00 g, 3.70 mmol) was dissolved in 2 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 0.554 mL, 4.24 mmol) and *tert*-butyl nitrite (0.504 mL, 4.24 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (420 mg, 4.24 mmol) in 3 mL of glacial acetic acid at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 200 mL of an ice/water slurry. The aqueous suspension was extracted with ether (2 x 200 mL) and the combined organic layers were washed twice with water (400 mL), washed once with saturated NaCl (400 mL), dried over sodium sulfate, filtered, and concentrated to 1.29 g (99 %) of a brown oil which was used directly in the next step without further purification.

c) 2-bromo-5-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide

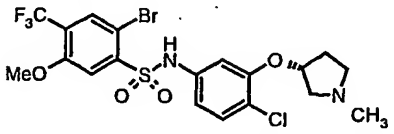


Aniline A (368 mg, 1.42 mmol) was dissolved in 10 mL of acetonitrile and treated with the product of Example 145b [2-bromo-5-(methyloxy)-4-(trifluoromethyl)benzenesulfonyl chloride] (500 mg, 1.42 mmol) and pyridine (0.458 mL, 5.66 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 3 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 50 mm, 50 mL/min, A: acetonitrile B:

water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 204.9 mg (25%) of the title compound as a pink solid. MS (ES) m/e 577 $[M+H]^+$

Example 146

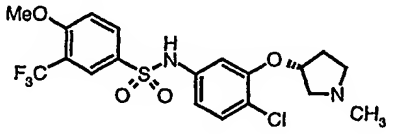
2-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-5-(methyloxy)-4-(trifluoromethyl)benzenesulfonamide



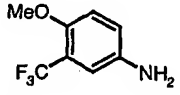
Aniline **B** (322 mg, 1.42 mmol) was dissolved in 10 mL of acetonitrile and treated with the product of Example 145b [2-bromo-5-(methyloxy)-4-(trifluoromethyl)benzenesulfonyl chloride] (500 mg, 1.42 mmol) and pyridine (0.458 mL, 5.66 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 3 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 50 mm, 50 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 170.9 mg (22%) of the title compound as a beige solid. MS (ES) m/e 543 $[M+H]^+$

Example 147

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(methyloxy)-3-(trifluoromethyl)benzenesulfonamide

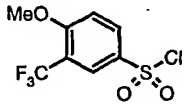


a) 4-(methyloxy)-3-(trifluoromethyl)aniline



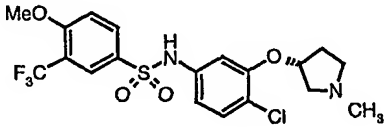
1-(methyloxy)-4-nitro-2-(trifluoromethyl)benzene (7.00 g, 31.7 mmol) was dissolved in 200 mL of methanol and the solution was degassed with argon. Then, the solution was treated with 10 % Pd on Carbon (1.05 g) and the flask was flushed with hydrogen gas. The reaction was stirred under an atmosphere of hydrogen for 18 hours, and then the mixture was filtered through Celite and concentrated to dryness under vacuum to give 5.70 g (94 %) of the product as a dark brown solid which was used in the next step without further purification.

b) 4-(methyloxy)-3-(trifluoromethyl)benzenesulfonyl chloride



The product of Example 147a [4-(methyloxy)-3-(trifluoromethyl)aniline] (500 mg, 2.62 mmol) was dissolved in 1 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 0.512 mL, 3.92 mmol) and *tert*-butyl nitrite (0.466 mL, 3.92 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (388 mg, 3.92 mmol) in 3 mL of glacial acetic acid at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 200 mL of an ice/water slurry. The aqueous suspension was extracted with ether (2 x 100 mL) and the combined organic layers were washed twice with water (200 mL), washed once with saturated NaCl (200 mL), dried over sodium sulfate, filtered, and concentrated to 298 mg (41 %) of an orange oil which was used directly in the next step without further purification.

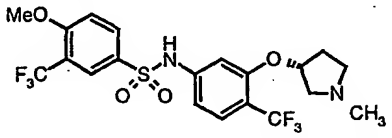
c) N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(methyloxy)-3-(trifluoromethyl)benzenesulfonamide



Aniline **B** (124 mg, 0.545 mmol) was dissolved in 2 mL of acetonitrile and treated with the product of Example 147b [4-(methyloxy)-3-(trifluoromethyl) benzenesulfonyl chloride] (149 mg, 0.543 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 50 mm, 50 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 91.9 mg (36%) of the title compound as a tan solid. MS (ES) m/e 465 $[M+H]^+$

Example 148

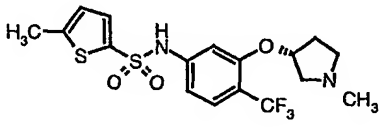
4-(methyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-3-(trifluoromethyl)benzenesulfonamide



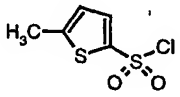
Aniline A (142 mg, 0.545 mmol) was dissolved in 2 mL of acetonitrile and treated with the product of Example 147b [4-(methyloxy)-3-(trifluoromethyl) benzenesulfonyl chloride] (149 mg, 0.543 mmol) and pyridine (1.0 mL, 12.4 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 2 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 50 mm, 50 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 73.0 mg (27%) of the title compound as a light brown solid. MS (ES) m/e 499 $[M+H]^+$

Example 149

5-Methyl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide

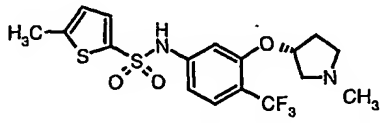


a) 5-methyl-2-thiophenesulfonyl chloride



A solution of 2-methylthiophene (507 mg, 5.16 mmol) in 5 mL of dichloromethane was added dropwise to a solution of chlorosulfonic acid (1.20 g, 10.3 mmol) in 5 mL of dichloromethane at –10 °C. The mixture was stirred at this temperature for 45 minutes and then poured onto an ice-water slurry and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to give 180 mg (18 %) of the product which was used directly in the next step without further purification.

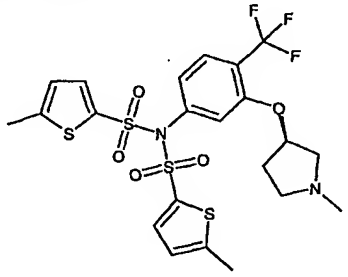
b) 5-Methyl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide



Aniline A (50 mg, 0.192 mmol) was dissolved in 2 mL of acetonitrile and treated with the product of Example 143a [5-methyl-2-thiophenesulfonyl chloride] (44 mg, 0.220 mmol) and pyridine (0.031 mL, 0.385 mmol) with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 1 mL of DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 32 mg (40%) of the title compound as a white microcrystalline solid. MS (ES) m/e 421 $[M+H]^+$

Example 150

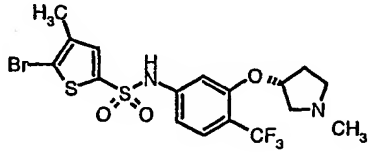
5-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-N-[(5-methyl-2-thienyl)sulfonyl]-2-thiophenesulfonamide



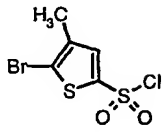
Also isolated from the reaction mixture of Example 149b [5-Methyl-thiophene-2-sulfonic acid [((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide], was the title compound (16 mg, 15%) as a separate fraction from the preparative HPLC. MS (ES) m/e 581 [M+H]+

Example 151

5-bromo-4-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-2-thiophenesulfonamide

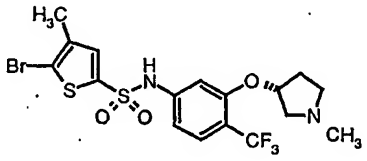


a) 5-bromo-4-methyl-2-thiophenesulfonyl chloride



A solution of 2-bromo-3-methylthiophene (531 mg, 3.00 mmol) in 10 mL of dichloromethane was added dropwise to a solution of chlorosulfonic acid (1.05 g, 9.00 mmol) in 10 mL of dichloromethane at 0 °C. The mixture was stirred at this temperature for 60 minutes and then poured onto an ice-water slurry and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to give 600 mg (73 %) of the product which was used directly in the next step without further purification.

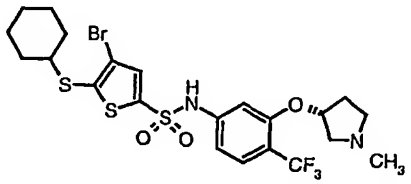
b) 5-bromo-4-methyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-2-thiophenesulfonamide



Aniline A (264 mg, 1.02 mmol) was dissolved in 6 mL of dichloromethane and pyridine (0.330 mL, 4.08 mmol) and treated with a solution of the product of Example 151a [5-bromo-4-methyl-2-thiophenesulfonyl chloride] (280 mg, 1.02 mmol) in 4 mL of dichloromethane with vigorous stirring at room temperature. The reaction mixture was maintained for 72 hours, and then the solvent was removed under reduced pressure. The residue was dissolved in 1 mL of DMSO and purified by reverse phase preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) and then further purified by normal phase preparative HPLC (Biotage Flash 12+M, KP-Sil, SiO_2, 12mm x 7.5 cm, 4 mL/min, A: MeOH, B: CH_2Cl_2, A: 5 to 15%, UV detection at 214 nm) to give 250 mg (47%) of the title compound as a white microcrystalline solid. MS (ES) m/e 499 $[M+H]^+$

Example 152

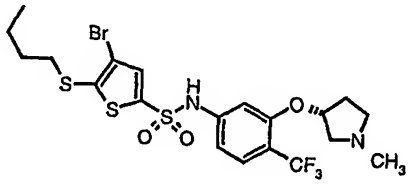
4-bromo-5-(cyclohexylthio)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide



4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide (50 mg, 0.096 mmol) was added as a solid to a mixture of cyclohexylmercaptan (0.013 mL, 0.106 mmol) and 3N NaOH solution (0.035 mL, 0.106 mmol) in DMF (1.0 mL) under argon with vigorous stirring. The reaction mixture was heated at 110 ° C for 16 h, and then at 140 °C for 3 days, after which time an additional amount of cyclohexylmercaptan (0.035 mL, 0.288 mmol) and 3N NaOH (0.096 mL, 0.288 mmol) was added and heated at 130 °C for an additional 18 hours. The reaction mixture was allowed to cool to room temperature, was filtered, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 10 to 90% over 10 min, UV detection at 214 nm) to give 14.9 mg (26 %) of the title compound as an oil. MS (ES) m/e 599 $[M+H]^+$

Example 153

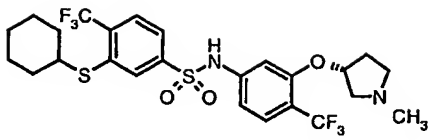
4-bromo-5-(butylthio)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide



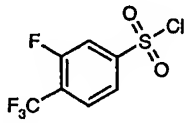
The title compound was prepared by a method similar to that of Example 152 [4-bromo-5-(cyclohexylthio)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-2-thiophenesulfonamide] except that butanethiol was used in place of cyclohexylmercaptan to give 11.5 mg (21%) of the title compound as an oil. MS (ES) m/e 573 $[M+H]^+$

Example 154

3-(cyclohexylthio)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide

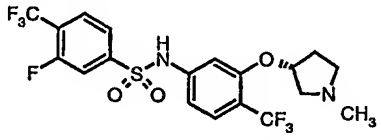


a) 3-fluoro-4-(trifluoromethyl)benzenesulfonyl chloride



3-fluoro-4-(trifluoromethyl)aniline (3.0 g, 16.8 mmol) was dissolved in 6 mL of acetonitrile, cooled to 0 °C, and treated with tetrafluoroboric acid (48% aqueous solution, 3.30 mL, 25.3 mmol) and *tert*-butyl nitrite (2.96 mL, 25.3 mmol). This reaction was maintained at 0 °C for one hour. In the meantime, a suspension of CuCl (2.50 g, 25.3 mmol) in 20 mL of acetonitrile at 0 °C was saturated with sulfur dioxide gas by bubbling the gas through the suspension with vigorous stirring for 30 minutes. When the diazotization reaction was complete after one hour, this solution was added dropwise to the suspension of CuCl, and the vigorous evolution of nitrogen gas was observed. The reaction was then allowed to warm to room temperature and stir for one hour, after which time it was poured onto 100 mL of an ice/water slurry. The product precipitated out of solution and the solid was dissolved in diethyl ether, dried over sodium sulfate, filtered, and concentrated to 4.31 g (97 %) of an amber oil which was used directly in the next step without further purification.

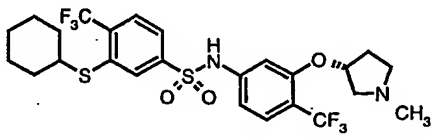
b) 3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide



A 25-mL round-bottom flask equipped with an argon inlet and a magnetic stirring bar was charged with 3.0 g (13.6 mmol) of Aniline A and 6 mL of anhydrous methylene chloride. The contents of the flask were stirred at room temperature until all of the solids were dissolved, and 2.2 mL of anhydrous pyridine was added. The solution was stirred for 60 sec before 4.31 mg (16.4 mmol) of the product of Example 154a [3-fluoro-4-(trifluoromethyl)benzenesulfonyl chloride] was added and the resulting mixture was stirred and maintained at room temperature for 18 hours. The solvent was removed by rotary evaporation at reduced pressure and the crude oil was dissolved in DMSO and purified by preparative HPLC (YMC CombiPrep ODS-A 50 x

20 mm, 20mL/min, A: acetonitrile B: water, 10 – 90% over 10 min, UV detection at 214 nm) to give 4.41 g (67%) of the product as a pale amber oil.

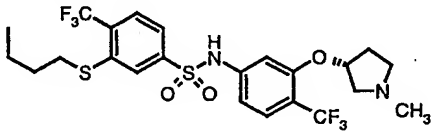
c) 3-(cyclohexylthio)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



The title compound was prepared by a method similar to that of Example 152 [4-bromo-5-(cyclohexylthio)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-2-thiophenesulfonamide] except that the product of Example 154b [3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl) benzene-sulfonamide] was used in place of 4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide to give 28 mg (47%) of the title compound as an oil. MS (ES) m/e 583 $[M+H]^+$

Example 155

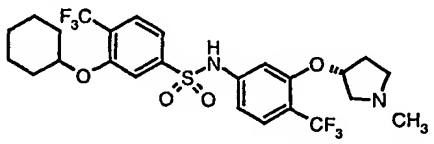
3-(butylthio)-N-[3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



The title compound was prepared by a method similar to that of Example 153 [4-bromo-5-(butylthio)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-2-thiophenesulfonamide] except that the product of Example 148b [3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl) benzene-sulfonamide] was used in place of 4-Bromo-5-chloro-thiophene-2-sulfonic acid [3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-amide to give 35 mg (61%) of the title compound as an oil. MS (ES) m/e 557 $[M+H]^+$

Example 156

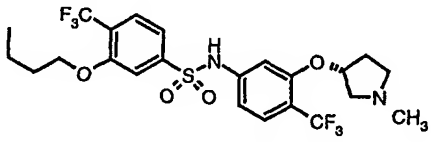
3-(cyclohexyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



The product of Example 154b [3-fluoro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(trifluoromethyl) benzenesulfonamide] (50 mg, 0.103 mmol), sodium hydride (95 %, 12 mg, 0.500 mmol), and cyclohexanol (0.048 mL, 0.462 mmol) were combined in 1 mL of DMSO and heated to 200 °C for 7.5 minutes in a sealed microwave vial with a Personal Chemistry Microwave Reactor at Normal Power. Then, an additional amount of sodium hydride (9.9 mg, 0.412 mmol) and cyclohexanol (0.43 mL, 0.412 mmol) were added and the reaction was heated again in the microwave to 200 °C for 15 minutes. The reaction mixture was allowed to cool to room temperature, was filtered, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 10 to 90% over 10 min, UV detection at 214 nm) to give 35.9 mg (62 %) of the title compound as an oil. MS (ES) m/e 567 $[M+H]^+$

Example 157

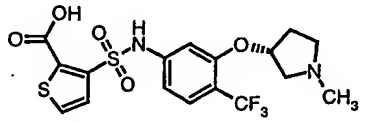
3-(butyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide



The title compound was prepared by a method similar to that of Example 156 [3-(cyclohexyloxy)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]-4-(trifluoromethyl)benzenesulfonamide] except that n-butanol was used in place of cyclohexanol to give 42 mg (62 %) of the title compound as an oil. MS (ES) m/e 541 $[M+H]^+$

Example 158

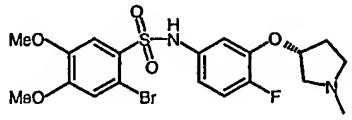
3-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-2-thiophenecarboxylic acid:



NaOH (2 mL, 1M) was added to a solution of the product of Example **107??** [methyl 3-({[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl) phenyl]amino}sulfonyl)-2-thiophenecarboxylate] and methanol (1 mL) and the mixture maintained at rt for 48 h. The mixture was concentrated in vacuo and the purified by preparative HPLC (Phenomenx Luna Combi-HTS 5 μ C_{18}, 75 x 30 mm, 40 mL/min, A: acetonitrile + 0.1% TFA, B: water + 0.1% TFA, A: 10 to 98% over 20 min, UV detection 214 nm) to provide the title compound as a solid. MS (ES) m/e 451.0 $[M+H]^+$.

Example 159

2-Bromo-*N*-(4-fluoro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide:



a) 5-Amino-2-fluorophenol

A solution of BBr_3 (d = 2.658, 973 μL, 10.01 mmol) in CH_2Cl_2 (5 mL) was added slowly (10 min) to a stirred solution of 2-fluoro-5-aminoanisole (483.7 mg, 3.43 mmol) in dichloromethane (5 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to ambient temperature, then stirred at that temperature for 18 h. The mixture was cooled in an ice-bath and cuatiously quenched with MeOH (20 mL), then evaporated *in vacuo* to a gummy residue. Redissolved the residue in MeOH (10 mL), re-evaporated *in vacuo* to the gummy residue, repeated the MeOH treatment two more times to expel the volatile borates. The resultant residue was dissolved in water (5 mL), saturated the solution with solid $NaHCO_3$, then extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried ($MgSO_4$), concentrated, in vacuo, to a crystalline solid (415.3 mg, 95%): mp 151-153 °C. MS m/e 128 $[M+H[^+$.

b) 4-Fluoro-3-hydroxyphenylcarbamic acid tert-butyl ester

A solution of di-*tert*-butyl dicarbonate (268.5 mg, 1.23 mmol) in THF (1.5 mL) was added to a solution of the product of Example 159a [5-amino-2-fluorophenol] (156.4 mg, 1.23 mmol) in THF (6 mL) at 0 °C. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, then the solvent was removed in vacuo to provide the title compound (271.4 mg, 97%) as a glassy solid. MS (ES) m/e 311.4 $[M+H]^+$.

c) (*R*)-[3-(1-Methyl-pyrrolidin-3-yloxy)-4-fluorophenyl]-carbamic acid

DIAD (d = 1.03, 487 µL, 2.39 mmol) was added to a cold (0 °C) solution of (*S*)-3-methyl-pyrrolidinol ((120.8 mg, 1.19 mmol), the product of Example 159b [2-fluoro-5-(*tert*-butoxy-crabomoyl)phenol] (271.4 mg, 1.19 mmol) and triphenylphosphine (626.5 mg, 2.39 mmol). The reaction mixture was warmed to room temperature and left standing at ambient temperature for 18 h. The solvent was removed *in vacuo* and the residue was partitioned in 1:1 EtOAc/10%HCl (20 mL). The aqueous phase was separated, washed 2x10 mL of EtOAc, then made basic (pH10) with 10% NaOH.The resulting precipitate was extracted with EtOAc, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to provide the desired product (359.1 mg, 97%) as a resin. MS (SE) e/m 311.4 $[M+H]^+$.

d) 4-Fluoro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline dihydrochloride

The product of Example 159c [(R)-[3-(1-methyl-pyrrolidin-3-yloxy)-4-fluorophenyl]-carbamic acid] (359.1 mg, 1.16 mmol) was dissolved in 1:1 TFA/DCM (3 mL), left standing at ambient temoperature for 18 h. The solvents were removed *in vacou*, dissolved the residue MeOH (2 mL) and treated with 1M Et_2O.HCl (3 mL) then evaporated *in vacuo* to provide the product as a solid. The crude product was triturated in DCM (5 mL) to provide a powdery solid, filtered under an argon atmosphere to give the product as the dihydrochloride salt (177.1 mg, 54%): mp 150-159 °C. MS (ES) e/m 211.2 $[M+H]^+$.

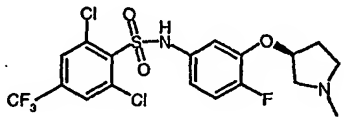
e) 2-Bomo-N-(4-fluoro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide

2-Bromo-4,5-dimethoxybenzenesulfonyl chloride (98.3 mg, 0.31 mmol) was added in one portion to a stirred suspension of the product of Example 159d [4-fluoro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy} aniline dihydrochloride] (88.3 mg, 0.31 mmol) and pyridine (d = 0.978, 76 µL, 0.94 mmol) in acetonitrile (0.5 mL). The mixture was heated at 60 °C for 1 h, cooled and purifired preparative HPLC (Phenomenx Luna Combi-HTS 5 µ C_{18}, 75 x 30 mm, 40 mL/min, A: acetonitrile + 0.1% TFA, B: water + 0.1% TFA, A: 10 to 98% over 20 min, UV detection

214 nm) to provide the product (144.3 mg) as the TFA salt. An aqueous solution (2 mL) of the TFA salt was made basic with saturated $NaHCO_3$ and the resulting gummy precipitate was crystallized from MeOH to provide the title compound (55.1 mg, 36%); mp 125-127 °C. MS (ES) m/e 489 $[M+H]^+$.

Example 160

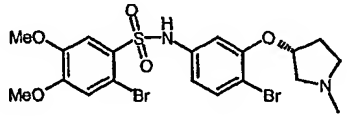
2,6-Dichloro-*N*-(4-fluoro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-(trifluoromethyl)benzenesulfonamide:



2,6-Dichloro-4-trifluoromethyl-benzenesulfonyl chloride was reacted with 4-fluoro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}aniline dihydrochloride in the exact manner as described in Example 159e to provide the title compound (61.3 mg, 43%): mp 92-95 °C. MS (ES) m/e 487 $[M+H]^+$.

Example 161

2-Bromo-*N*-(4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide



a) 2-Bromo-5-nitrophenol

A solution of BBr_3 (d = 2.658, 1.62 mL, 17.24 mmol) CH_2Cl_2 (5 mL) was added slowly (~15 min) to a stirred, cold (0 °C), solution of 2-bromo-5-nitroanisole (1.00 g, 4.31 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere. The mixture was allowed to warm room temperature and left standing at ambient temperature for 18 h. The mixture was cooled in an ice-bath and quenched, cautiously, with MeOH (15 mL). The mixture was concentrated to ~10 mL on a steam bath, replenished with MeOH (15 mL), reconcentrated to ~10 mL, repeated the MeOH process two more times to ensure the removal of the volatile borates, finally the solvent was removed in vacuo to provide the crude product as a solid (1.04 g). The solid was dissolved in 2.5N NaOH (~5 mL), filtered to remove 0.11 g of the starting anisole. The filtrate was acidified (pH 1) with conc. HCl and the resulting precipitate was filtered to provide 0.62 g of product. The material was purified by flash chromatography (Varian Bond Elute 10g Si

cartridge, CH_2Cl_2) to provide clean product (0.54 g, 65%); mp 115-117 °C. MS (ES) m/e 218 $[M+H]^+$.

b) (*3R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine

A solution of the product of Example 161a [2-bromo-5-nitrophenol] (1.2214 g, 5.50 mmol), (*S*)-3-methyl-pyrrolidinol (0.5668 g, 5.60 mmol), and triphenylphosphine (2.939 g, 11.20 mmol) in THF (20 mL) was treated with DIAD (d = 1.03, 2.2 mL, 11.20 mmol) in the exact manner as described Example 161c. Isolated 1.03 g (61%) of product as a solid. MS (ES) m/e 301.2 $[M+H]^+$.

c) 4-Bromo-3-{[(*3R*)-1-methyl-3-pyrrolidinyl]oxy}aniline

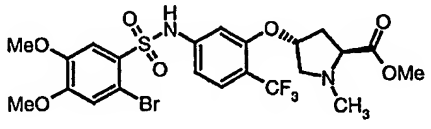
A mixture of the product of Example 161b [(3*R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine] (0.3011g, 1.0 mmol) and $SnCl_2.2H_2O$ (1.1282 g, 5.0 mmol)in EtOH (3.85 mL) was heated at 70 °C for 0.5 h, cooled and adjusted to pH10-11 with 2.5N NaOH forming a gummy precipitate. The mixture was extracted EtOAc (3x10 mL), and the combined extracts were washed with water (10 mL), brine, dried ($MgSO_4$), removed the solvent in vacuo to the product (0.2095 g, 77%) as a syrup. ME (ES) m/e 271 $[M+H]^+$.

d) 2-Bromo-N-(4-bromo-3-{[(*3R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4,5-bis(methyloxy)benzenesulfonamide

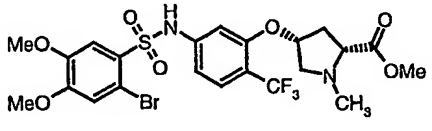
The procedure in Example 159e was used to prepare the title compound. Isolated 34.9 mg (8%): mp 168-170 °C. MS (ES) m/e 549 $[M+H]^+$.

Example 162

N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide and N-[3-(1-methyl-2(R)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:



and



a) 3-Fluoro-4-trifluoromethylnitrobenzene:

3-Fluoro-4-trifluoromethylaniline (15.10 g, 85.4 mmole) was dissolved on CF_3CO_2H (85 ml). H_2O_2 (50% in H_2O, 42 ml 1.46mole, 7 eq) was added dropwise over 35 min. The mixture was stirred and heated at 45°C for 2 hr and 65°C for 40 min before being cooled to rt and poured into ice/water (600 ml). The mixture was stirred overnight. Ether (250 ml) was added and the organic layer was separated. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, twice with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow oil (17.10 g, 96%).

b) 3-[2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl nitrobenzene:
A solution of the compound of Example 162a (3.14 g, 15 mmole) and 2(S)3(R)-N-*tert*-butoxycarbonylhydroxyproline methyl ester (3.68g, 15 mmole) in dry THF (75 ml) was cooled to 0°C and then NaH (60% in mineral oil, 1.20 g, 30 mmole) was added protionwise over 5 min. The mixture was stirred and allowed to warm to rt. Once at rt, the mixture was stirred an additional 2 hr. The solvent was removed under reduced pressure and then the residue was dissolved in MeOH (75 ml). 4M HCl in dioxane (20 ml) was added and the resultant mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The aqueous layer was adjusted to pH 7 using aqueous Na_2CO_3 and then was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated to give the title compound as a yellow oil (2.50 g, 50%). MS (ES) m/e 335.2 $[M+H]^+$.

c) 3-[1-methyl-2(R/S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl nitrobenzene:
The compound of Example 162b (3.20 g, 9.6 mmole) and formaldehyde (37% wt. in water, 0.94 g, 11.5 mmole, 1.2 eq) was dissolved in CH_2Cl_2 (70 ml). $Na(OAc)_3BH$ (3.01 g, 14.4 mmole, 1.5 eq) was added and the resultant mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was purified by column chromatography (150 g silica gel 60, 230-400 mesh, CH_2Cl_2 then 1% MeOH in CH_2Cl_2 then 2% MeOH in CH_2Cl_2 as eluent) to give 2.80 g (73%) of a mixture of diastereomers as a yellow oil. MS (ES) m/e 349.0 $[M+H]^+$.

d) 3-[1-Methyl-2(R/S)-methoxycarbonylpyrrolidin-3(R)-yloxy]-4-trifluoromethyl aniline:

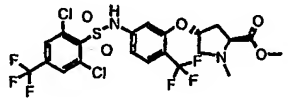
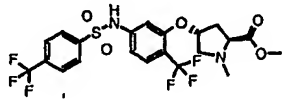
Pd-C (10 %, 0.9g) added to a solution the compound of Example 162c (1.96 g, 5.6 mmol) and MeOH (50 mL). The resulting mixture was shaken under a H_2 atmosphere (50 psi) for 3h. The mixture was then filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give 1.8 g (100%) of the title compound as a tan oil. MS (ES) m/e 319.2 $[M+H]^+$.

e) N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide and N-[3-(1-methyl-2(R)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:

Pyridine (0.48 g, 6.0 mmol), followed by the compound of Example 162d (1.9 g, 6.0 mmol) was added to a solution of 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (1.9 g, 6.0 mmol) and acetonitrile (30 mL). The resultant mixture was stirred at rt overnight. The mixture was concentrated and purified by purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 10 to 90% over 10 min, UV detection at 214 nm) to give silica gel chromatography. Mixed fractions were further purified by purified by column chromatography (140 g silica gel 60, 230-400 mesh, 1-3% methanol in CH_2Cl_2 as eluent) to give to give 1.2 g (34%) of N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide. MS (ES^+) m/e 597.2 $[M+H]^+$. and 0.27 g (8%) of N-[3-(1-methyl-2(R)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide. MS (ES) m/e 597.2 $[M+H]^+$.

Examples 163-164

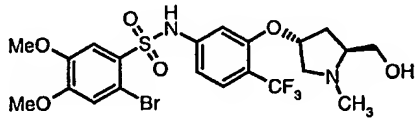
Using the procedure outlined in Example 162e, the following compounds were prepared.

#	structure	name	m/z
163		N-[3-(1-Methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2,6-dichloro-4-trifluoromethylbenzenesulfonamide	595
164		N-[3-(1-Methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4-	527

		trifluoromethylbenzenesulfonamide	

Example 165

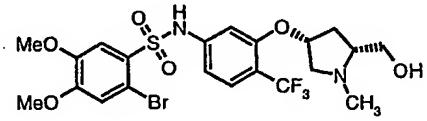
N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:



$LiBH_4$ (0.24 g, 1.1 mmol) was added to a solution of the compound of Example 162 (0.6 g, 1.0 mmol) and THF (10 mL) and the resultant mixture was stirred at rt overnight. The mixture was then diluted with MeOH and concentrated. The residue was dissolved in MeOH (10 mL), 2N HCl was added (10 mL) and the solution allowed to stand overnight. The solution was then concentrated in vacuo and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 100 mg (17%) of the title compound as a white solid. MS (ES) m/e 569.2 $[M+H]^+$.

Example 166

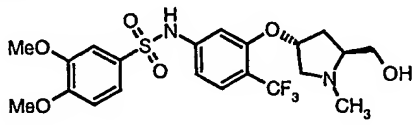
N-[3-(2(R)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:



$LiBH_4$ (24 mg, 0.11 mmol) was added to a solution of the compound of Example 162 (60 mg, 0.1 mmol) and THF (1 mL). The resultant mixture was stirred at rt overnight. Satd NH_4Cl was added and the mixture extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and 2N HCl (2 mL) and stirred overnight. The mixture was concentrated under reduced pressure and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 4.4 mg (8%) of the title compound as a tan oil. MS (ES) m/e 569.2 $[M+H]^+$.

Example 167

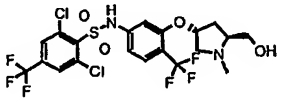
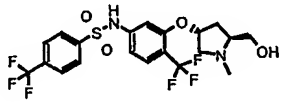
N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-3,4-dimethoxybenzenesulfonamide:



A solution of the compound of Example 162 (0.30 g, 0.50 mmol) and THF (2mL) was added dropwise to a solution of 1 M $LiAlH_4$ in ether (1.0 mL, 1.0 mmol). The mixture was stirred at rt for 20 min and then another portion of $LiAlH_4$ (2.0 mL, 2.0 mmol) was added. The mixture was stirred an additional 45 min before being quenched with water (0.22 mL) and NaF (0.38 g, 9.1 mmol). The mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo. The residue was purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 35 mg (14%) of the title compound as a tan solid. MS (ES) m/e 491.2 $[M+H]^+$.

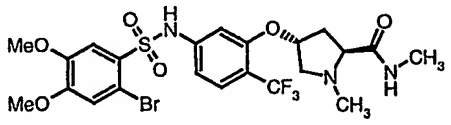
Example 168-169

Using the procedure outlined in Example 161, the following compounds were prepared.

#	structure	name	m/z
168		N-[3-(2(S)-Hydroxymethyl-1-methypyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2,6-dichloro-4-trifluoromethylbenzenesulfonamide	567
169		N-[3-(2(S)-Hydroxymethyl-1-methypyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4-trifluoromethylbenzenesulfonamide	499

Example 170

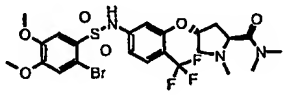
N-[3-(1-Methyl-2(S)-N-methylamidepyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4,5-dimethoxybenzenesulfonamide:



NaOH (40 mL, 1 M) was added to a solution of the compound of Example 162 (1.24 g, 2.08 mmol) and methanol (20 mL). The resultant mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was partitioned between water and CH_2Cl_2 and acidified to pH = 3-4. The layers were separated and the aqueous washed with two more portions of CH2Cl2. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to give 0.83 g of carboxylic acid. 200 mg (0.34 mol) of this product and methylamine (2 M in THF, 0.20 mL, 0.41 mol) were dissolved in MeCN (2 mL). BOP reagent (150 mg, 0.34 mmol) and triethylamine (34 mg, 0.34 mmol) were added. The resultant mixture was stirred at rt for 16 h and then concentrated in vacuo. The redidue was partitioned between EtOAc and 5% aqueous Na2CO3. The organic layere was separated, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel chromatography (35 g Redisep column, silica, 40 um, 60 Å, 35 mL/min, A: MeOH, B: CH_2Cl_2, A: 0-1% for 25 min, 1-2% for 30 min, 2% for 10 min; detection at 214 nm) to give 90 mg (44%) of the title compound as a white solid. MS (ES) m/e 596.0 $[M+H]^+$.

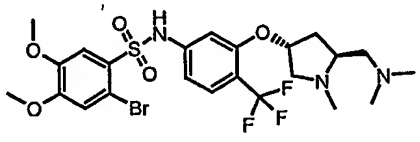
Example 171

Using the procedure of Example 164, the following compound was prepared:

#	structure	name	m/z
171		N-[3-(1-Methyl-2(S)-N,N-dimethylamidepyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-boromo-4,5-dimethoxybenzenesulfonamide	610

Example 172

N-[3-(1-Methyl-2(S)-N,N-dimethylmethylamidepyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-boromo-4,5-dimethoxybenzenesulfonamide:

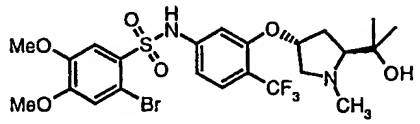


Borane methylsulfide (2 M, 0.1 mL, 0.2 mmol) was added dropwise to a solution of the compound of Example 165 (20 mg, 0.033 mmol) and THF (2 mL). The resultant mixture was stirred at rt for 16 h before being concentrated in vacuo. The crude mixture was purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B:

water, A: 10 to 90% over 10 min, UV detection at 214 nm) to give 18 mg (93%) of the title compound as a clear oil. MS (ES) m/e 596.2 $[M+H]^+$.

Example 173

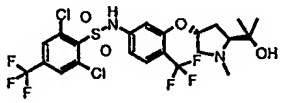
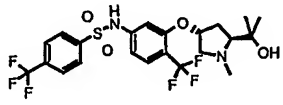
N-[3-(2(S)-2,2-dimethylhydroxymethyl-1-methypyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide:



MeMgBr (3 M in ether, 0.40 mL, 1.2 mmol) was added to a solution of the product from Example 156 (0.12 g, 0.20 mmol) and THF (2 mL). The resultant mixture was maintained at rt for 2 h then quenched with water. The mixture was extracted with CH_2Cl_2 and then ether. The organic layers were combined, dried ($MgSO_4$) and concetrated in vacuo. The crude product was purfied by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A:10 to 90% during 10 min, UV detection at 214 nm) to give 22 mg (18%) of the title compound as a tan oil. MS (ES) m/e 597.0 $[M+H]^+$.

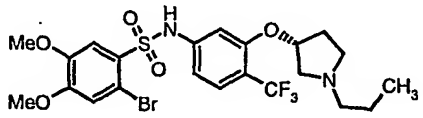
Example 174-175

Using the procedure of Example 167, the following compounds were prepared:

#	structure	name	m/z
174		N-[3-(2(S)-2,2-dimethylhydroxymethyl-1-methypyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2,6-dichloro-4-trifluoromethylbenzenesulfonamide	595
175		N-[3-(2(S)-2,2-dimethylhydroxymethyl-1-methypyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4-trifluoromethylbenzenesulfonamide	527

Example 176

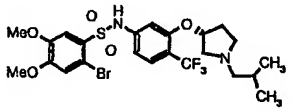
2-Bromo-4,5-dimethoxy-N-[3-((R)-1-propyl-pyrrolidin-3-yloxy)-4- trifluoromethyl-phenyl]-benzenesulfonamide:



To a mixture of N-[4-Trifluoromethyl-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide hydrochloride (75 mg, 0.133 mmole) and propionaldehyde (10 uL, 8 mg, 0.133 mmole) in EtOH (3 mL), was added $NaBH_3CN$ (11 mg, 0.173 mmole).. The mixture was stirred at rt 18 hr. Solvent was evaporated and the mixture chromatographed on a normal-phase Gilson Automated Chromatography System using a solvent gradient of dichloromethane to 15% methanol- dichloromethane as elutant to provide 60 mg (80%) of the title compound. MS (ES) m/e 567 $[M+H]^+$.

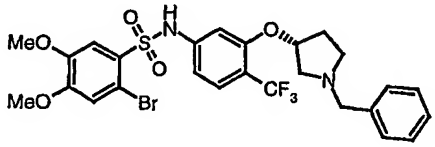
Example 177

Following the procedure of Example 176, except substituting isobutyraldehyde for propionaldehyde gave the following compound:

#	structure	name	m/z
177		2-Bromo-N-[3-((R)-1-isobutyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4,5-dimethoxy-benzenesulfonamide	581

Example 178

N-[3-((R)-1-Benzyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-2-bromo-4,5-dimethoxy-benzenesulfonamide:

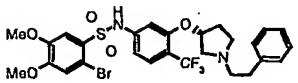
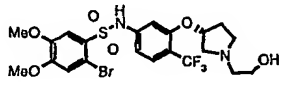
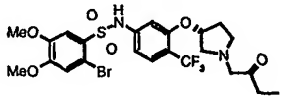
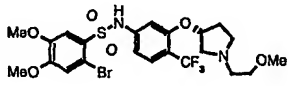


To a mixture of N-[4-Trifluoromethyl-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide hydrochloride (75 mg, 0.133 mmol), K_2CO_3 (55 mg, 0.4 mmol), and KI (22 mg, 0.133 mmol) in CH_3CN (2 mL), was added benzyl bromide (17 uL, 25 mg, 0.146 mmol). The mixture was stirred at rt 18 hr. Solvent was evaporated and the mixture

chromatographed on a normal-phase Gilson Automated Chromatography System using a solvent gradient of dichloromethane to 15% methanol- dichloromethane as elutant to obtain 40 mg (50%) of the title compound. MS (ES) m/e 615 $[M+H]^+$.

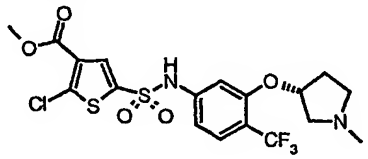
Examples 179-182

Following the procedure of Example 178, except substituting phenethyl bromide, bromoethanol, 1-bromo-2-butanonone and 2-methoxyethyl bromide for benzyl bromide gave the following compounds:

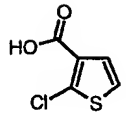
#	structure	name	m/z
179		2-Bromo-4,5-dimethoxy-N-[3-((R)-1-phenethyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	629
180		2-Bromo-N-{3-[(R)-1-(2-hydroxy-ethyl)-pyrrolidin-3-yloxy]-4-trifluoromethyl-phenyl}-4,5-dimethoxy-benzenesulfonamide	569
181		2-Bromo-4,5-dimethoxy-N-{3-[(R)-1-(2-oxo-butyl)-pyrrolidin-3-yloxy]-4-trifluoromethyl-phenyl}-benzenesulfonamide	595
182		N-[3-((R)-1-methoxyethylpyrrolidin-3-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	583

Example 183

Methyl 2-chloro-5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-thiophenecarboxylate:

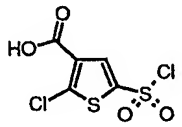


a) 2-chloro-3-thiophenecarboxylic acid



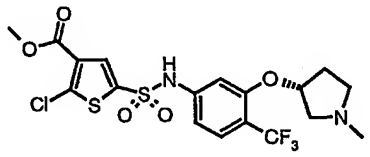
A solution of 3-bromo-2-chlorothiophene (3.3 g, 17 mmol) in dry THF (20 mL) was added dropwise to a solution of *n*-butyllithium (7.4 mL, 1.6M in hexane) in dry THF (10mL) at –78°C under Argon. After stirring for 15 min, the reaction mixture was poured into crushed dry ice covered with ether. When the temperature had risen to 0°C, sodium hydroxide (2N, 150 mL) was added. The ether phase was extracted with sodium hydroxide (x3) and the combined aqueous was cooled at 0°C and acidified with 6N HCl. The product precipated and was collected by filtration; drying left 2.1 g (76%) as a white solid.

b) 2-chloro-5-(chlorosulfonyl)-3-thiophenecarboxylic acid



The product of Example 183a [2-chloro-3-thiophenecarboxylic acid] (2.1 g , 14.6 mmol) was added slowly to chlorosulphonic acid (5.1 mL, 5.2 equiv.) at 0°C. The resulting mix was then heated at 95°C for 2h. After cooling, the mix was poured into ice (Caution, Slow!!). The product was collected by filtration; drying left 2.67 g (71% yield). IR (film) 1377.97 cm^{-1} and 1161.23 cm^{-1}.

c) Methyl 2-chloro-5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-thiophenecarboxylate:

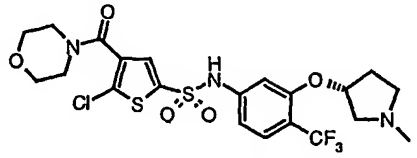


A solution of the product sulfonyl chloride from Example 183b (1.30g, 5 mmol) in CH_2Cl_2 (20mL) was added dropwise to a solution containing Aniline A (1.3 g, 5 mmol) and pyridine (1.6 mL, 20 mmol) in CH_2Cl_2 (25 mL) over 60 min. The resulting mixture was stirred at rt for 18h. The reaction mix was concentrated in vacuo, which left an orange yellow solid (pyridinium salt) which was refluxed in MeOH saturated with HCl (30 ml) for 18h. The mixture was concentrated and the residue was dissolved in EtOAc and washed with 10%

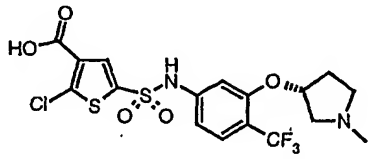
$NaHCO_3$, saturated NaCl, dried ($MgSO_4$) and concentrated. Purificaiton by silica gel chromatography (1-3% MeOH in CH_2Cl_2) gave 980mg of the title compound as a white solid. MS (ES) m/e 499 $[M+H]^+$.

Example 184

5-Chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(4-morpholinylcarbonyl)-2-thiophenesulfonamide:

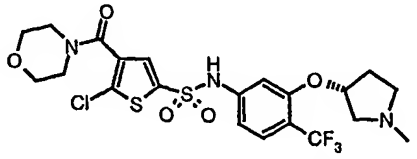


a) 2-chloro-5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-thiophenecarboxylic acid:



A solution of the sulfonyl chloride from Example 183b (1.30 g, 5 mmol) in CH_2Cl_2 (20mL) was added dropwise to a solution containing Aniline A (1.3 g, 5 mmol) and pyridine (1.62 mL, 20 mmol) in CH_2Cl_2 (25 mL) over 60 min., the resulting mix was stirred at rt for 18h. The reaction mix was concentrated in vacuo which left an orange yellow solid (pyridinium salt) which was used as without further purification. MS (ES) m/e 485.0 $[M+H]^+$.

b) 5-Chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(4-morpholinylcarbonyl)-2-thiophenesulfonamide

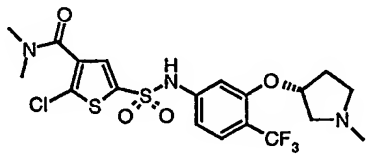


A mixture of the carboxylic acid from Example 184a (242 mg, 0.5 mmol), morpholine (44 mg, 0.5 mmol), DIEA (96 ul, 0.55 mmol) and BOP (232 mg, 0.55 mmol) in DMF (2mL) was stirred at rt for 18 h. The reaction was concentrated invacuo and the reside was taken up in EtOAc and washed with water, saturated NaCl, dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC (Xterra Prep RP, 75 x 30 mm, 25 mL/min, A: acetonitrile(containing 0.1% TFA) B: water (containing 0.1%TFA), A:5- to 50% during 15min, UV detection at 214

nm). The product was then treated with HCl (1M in ether) to give the title compound as its HCl salt which was a light yellow solid. MS (ES) m/e 554.4 $[M+H]^+$.

Example 185

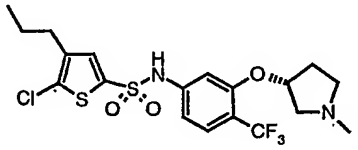
2-Chloro-*N*,*N*-dimethyl-5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-3-thiophenecarboxamide:



Following the procedure of Example 184b replacing morpholine by dimethylamine gave the title compound as HCl salt which was a pale yellow solid. MS (ES) m/e 512.2 $[M+H]^+$.

Example 186

Preparation of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-propyl-2-thiophenesulfonamide:

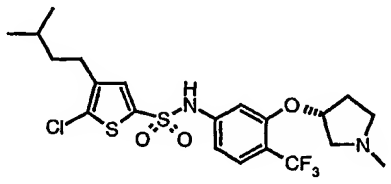


n-BuLi (1.9 mL; 1.6 M in hexane) was added dropwise to a solution of 3-bromo-2-chlorothiophene (550 mg, 2.8 mmol) in dry THF(10 mL) at –78°C under argon. The resulting mixture was stirred at–78°C for 5 min. then 1-iodopropane (2.4 g, 13.9 mmol) was added .The mixture was stirred at –78°C for another 15 min. and then was quenched by adding water. The reaction mix was extracted with ether and the ether extracts were washed with saturatd NaCl, dried ($MgSO_4$) and concentrated to a light yellow solid. Chlorosulfonic acid (739 □l, 11 mmol) was then added dropwise to a solution of this material in CH_2Cl_2 (28 mL) at room temperature The resulting mixture was stirred at rt for 18 h. The mixture was concentrated and azetroped with toluene (x2) to remove excess chlorosulfonic acid and kept in vacuum for several hours. The crude mixture was then dissolved in CH_2Cl_2 (28 mL) and added dropwise to a mixture containing Aniline A (1.4g, 2.78 mmol) and pyridine (899 uL, 11.2 mmol). After stirring at rt for 18 h, the mixture was concentrated invacuo and the residue redissolved in CH_2Cl_2, washed with water then saturated NaCl, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (0-5% MeOH in CH_2Cl_2) to give 202 mg

which was further purified by preparative HPLC (Xterra Prep RP, 75 x 30 mm, 25 mL/min, A: acetonitrile containing 0.1% TFA, B: water containing 0.1%TFA, A:5- to 75% during 15min, UV detection at 214 nm). The product was treated with HCl (1M in ether) to give the HCl salt as a pale yellow solid. MS (ES) m/e 483.2 $[M+H]^+$.

Example 187

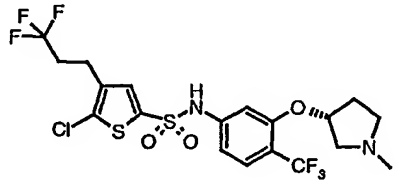
5-chloro-4-(3-methylbutyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide:



Following the procedure of Example 186, replacing 1-iodopropane by 1-iodo-3-methylbutane gave the title compound as a pale yellow solid. MS (ES) m/e 511.2 $[M+H]^+$.

Example 188

5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-(3,3,3-trifluoropropyl)-2-thiophenesulfonamide:

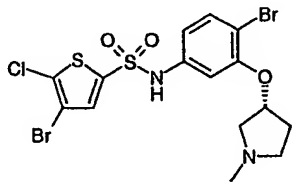


t-BuLi (0.44mL, 1.7 M in pentane, 0.748 mmol) was added rapidly to a solution of 3,3,3-trifluoro-1-iodo-propane (78 mg, 0.35 mmol) in Et_2O (5 mL) at -78°C. After 3 min, 9-methoxy-9-BBN (0.82 mL, 1.0 M in THF, 0.82 mmol) was added followed by THF (5mL). The solution was stirred at –78°C for 10 min then allowed to warm to room temperature (1.5 h). Aqueous K_3PO_4 (0.27 mL, 3 M, 0.81 mmol) was added followed by the addition of 4-bromo-5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (83 mg, 0.16 mmol) in DMF (2 mL) and Pd (dppf)Cl_2. (13 mg, 0.016 mmol). The resulting mixture was heated at 60°C for 18 h. The reaction mixture was concentrated invacuo and the residue was dissolved in EtOAc washed with water, saturated NaCl, dried ($MgSO_4$) and concentrated. Purificaiton by dilica gel chromatographgy (1-4% MeOH in CH_2Cl_2) gave100 mg which was further purified by preparative HPLC (Xterra Prep

RP, 75 x 30 mm, 25 mL/min, A: acetonitrile containing 0.1% TFA, B: water containing 0.1%TFA, A: 5- to 72% during 14min, UV detection at 214 nm): The product was then treated with HCl (1M in ether) to give the title compounds as its HCl salt as a pale yellow solid. MS (ES) m/e 536.0 $[M+H]^+$.

Example 189

4-bromo-*N*-(4-bromo-3-{[(3*R*)-1-methylpyrrolidin-3-yl]oxy}phenyl)-5-chlorothiophene-2-sulfonamide



Tribromoborane (25 g, 100 mmol) was added dropwise to a solution of 2-bromo-5-nitroanisole (7.94 g, 34.2 mmol) in methylene chloride (100 mL) at 0 °C. The solution was allowed to warm to room temperature and react for 16 h. The reaction was then quenched by the addition of methanol (20 mL) and stirred for 3 h. The solvent was removed under reduced pressure and the remaining residue purified by column chromatography (400 g silica gel 60, 230-400 mesh, 5-20% ethyl acetate/hexanes as eluent) to give 2-bromo-5-nitrophenol (6.2 g, 83%). MS (ES) m/e 217.6 $[M+H]^+$.

Diisopropyl azodicarboxylate (3.34 g, 16.5 mmol) was added dropwise to a solution of 2-bromo-5-nitrophenol (3.0 g, 13.8 mmol), (3*S*)-1-methyl-3-pyrrolidinol (1.4 g, 13.8 mmol), and triphenylphosphine (4.33 g, 16.5 mmol) in methylene chloride (100 mL). The reaction was maintained for 16 h at room temperature. The solvent was removed under reduced pressure and the remaining material purified by column chromatography (300 g silica gel 60, 230-400 mesh, 0-5% methanol/methylene chloride as eluent) to provide (3*R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine (2.6 g, 63%). MS (ES) m/e 301.2 $[M+H]^+$.

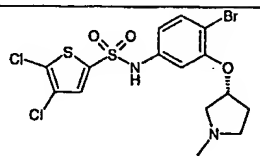
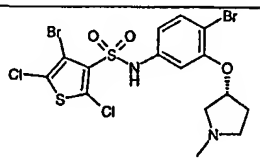
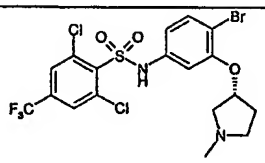
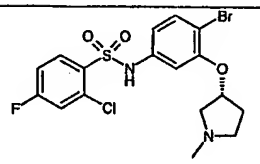
A mixture of iron (5 g) and iron (III) chloride (5 g) was added to a solution of (3*R*)-3-[(2-bromo-5-nitrophenyl)oxy]-1-methylpyrrolidine (2.2 g, 7.3 mmol) in acetic acid (15 mL) and water (5 mL). After stirring for 18 h at room temperature, the mixture was filtered and concentrated. The remaining residue was dissolved in aqueous hydrochloric acid (6 mL of a 2 M aqueous solution) and ethyl acetate (10 mL). The layers were separated and the organic

layer discarded. The aqueous layer was concentrated to give 4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline as a hydrochloride salt (2.2 g, 100%). MS (ES) m/e 271.2 $[M+H]^+$.

A solution of 4-bromo-5-chloro-2-thiophenesulfonyl chloride (382 mg, 1.29 mmol) in methylene chloride (2 mL) was added to a solution of 4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline (350 mg, 1.29 mmol) and pyridine (306 mg, 3.87 mmol) in methylene chloride (8 mL) at –78 °C. After 1 h, the solution was allowed to warm to room temperature and stir for 15 h. The volatiles were removed under reduced pressure and the remaining crude material was purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (16 mg, 28%) as a trifluoroacetate salt. MS (ES) m/e 529.0 $[M+H]^+$.

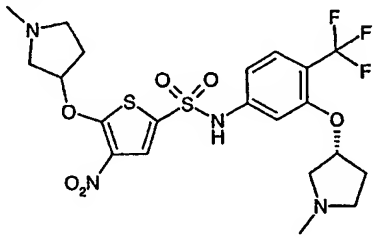
Examples 190-193

The following examples were prepared in an analogous fashion to the representative procedure in Example 189 using the appropriate sulfonyl chlorides as starting material.

#	structure	name	m/z
190		*N*-(4-bromo-3-{[(3*R*)-1-methylpyrrolidin-3-yl]oxy}phenyl)-4,5-dichlorothiophene-2-sulfonamide	485.0
191		4-bromo-*N*-(4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,5-dichloro-3-thiophenesulfonamide	566.2
192		*N*-(4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2,6-dichloro-4-(trifluoromethyl)benzenesulfonamide	549.0
193		*N*-(4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-2-chloro-4-fluorobenzenesulfonamide	463.2

Example 194

5-[(1-methyl-3-pyrrolidinyl)oxy]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-



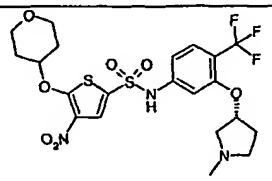
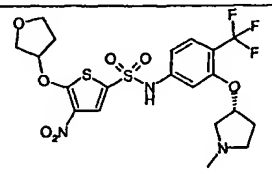
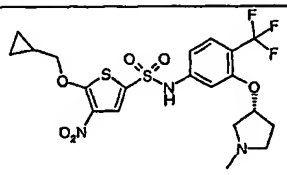
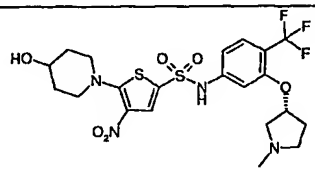
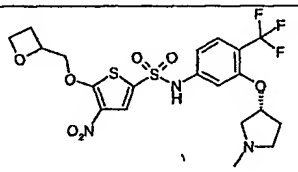
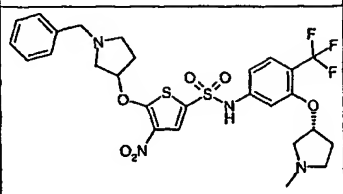
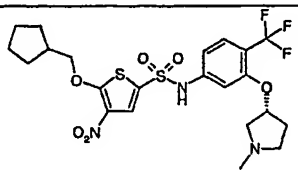
(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide

A solution of 5-chloro-4-nitro-2-thiophenesulfonyl chloride (1.0 g, 3.82 mmol) in methylene chloride (5 mL) was added to a solution of 3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)aniline (0.83 g, 3.18 mmol) and pyridine (0.76 g, 9.54 mmol) in methylene chloride (20 mL) at –78 °C. The solution was allowed to warm to room temperature and stir for 16 h. The volatiles were removed *in vacuo* and the remaining crude material purified by column chromatography (250 g silica gel 60, 230-400 mesh, 5-25% methanol/methylene chloride as eluent) to provide 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (500 mg, 33%). MS (ES) m/e 486.0 $[M+H]^+$.

To a mixture of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (50 mg, 0.10 mmol) and cesium carbonate (134 mg, 0.41 mmol) in dimethylformamide (1 mL) was added 1-methyl-3-pyrrolidinol (16 mg, 0.15 mmol). The reaction was allowed to stir for 18 h. The mixture was filtered through a 0.45 μm fritted funnel and the remaining material purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (6.1 mg, 9%) as a trifluoroacetate salt and a mixture of diastereomers. MS (ES) m/e 551.2 $[M+H]^+$.

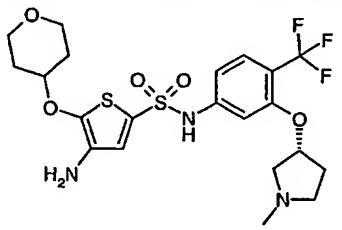
Examples 195-201

The following examples were prepared according to the representative procedure in Example 194 using the appropriate alcohols as starting material. For some of the alcohol starting materials, the reactions required heating the dimethylformamide solution at 50 °C for 16 h.

#	structure	name	m/z
195		*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(tetrahydro-2*H*-pyran-4-yloxy)-2-thiophenesulfonamide	551.8
196		*N*-[3-{[(3*R*)-1-methylpyrrolidin-3-yl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(tetrahydrofuran-3-yloxy)thiophene-2-sulfonamide	538.2
197		5-[(cyclopropylmethyl)oxy]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	522.2
198		5-(4-hydroxy-1-piperidinyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	551.0
199		*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-[(2-oxetanylmethyl)oxy]-2-thiophenesulfonamide	538.2
200		*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-{[1-(phenylmethyl)-3-pyrrolidinyl]oxy}-2-thiophenesulfonamide	627.2
201		5-[(cyclopentylmethyl)oxy]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide	550.2

Example 202

4-amino-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5-(tetrahydro-

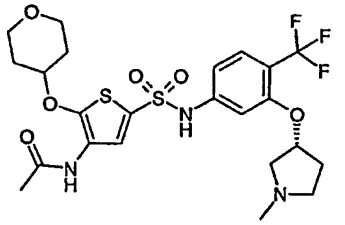


2*H*-pyran-4-yloxy)-2-thiophenesulfonamide

A mixture of *N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(tetrahydro-2*H*-pyran-4-yloxy)-2-thiophenesulfonamide (8.2 mg, 0.012 mmol) and iron powder (spatula tip) in acetic acid (1 mL) was allowed to stir at room temperature for 18 h. The mixture was filtered and the remaining residue purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (1.7 mg, 18%) as a trifluoroacetate salt. MS (ES) m/e 522.2 $[M+H]^+$.

Example 203

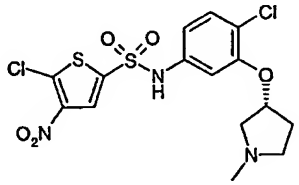
N-[5-({[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]amino}sulfonyl)-2-(tetrahydro-2*H*-pyran-4-yloxy)-3-thienyl]acetamide



To a solution of *N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-5-(tetrahydro-2*H*-pyran-4-yloxy)-2-thiophenesulfonamide (10 mg, 0.018 mmol) and acetic anhydride (0.5 mL) in acetic acid (2 mL) was added excess iron powder (spatula tip) and a catalytic amount of iron (III) chloride (spatula tip). The mixture was allowed to stir at room temperature for 18 h. The mixture was filtered and the remaining residue purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (4.4 mg, 36%) as a trifluoroacetate salt. MS (ES) m/e 564.2 $[M+H]^+$.

Example 204

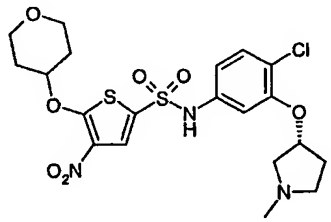
5-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-nitro-2-thiophenesulfonamide



A solution of 5-chloro-4-nitro-2-thiophenesulfonyl chloride (230 mg, 0.88 mmol) in methylene chloride (2 mL) was added to a solution of 4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}aniline (200 mg, 0.88 mmol) and pyridine (210 mg, 2.6 mmol) in methylene chloride (8 mL). The solution was maintained at room temperature for 16 h. The volatiles were removed under reduced pressure and the remaining residue dissolved in dimethylformamide, filtered through a 0.45 um fritted funnel, and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (40 mg, 8%) as a trifluoroacetate salt. MS (ES) m/e 452.0 $[M+H]^+$.

Example 205

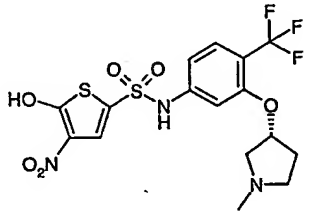
N-(4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-nitro-5-(tetrahydro-2*H*-pyran-4-yloxy)-2-thiophenesulfonamide



To a mixture of 5-chloro-*N*-(4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-nitro-2-thiophenesulfonamide (25 mg, 0.044 mmol) and cesium carbonate (215 mg, 0.66 mmol) in dimethylformamide (1 mL) was added tetrahydro-2*H*-pyran-4-ol (45 mg, 0.44 mmol). The mixture was allowed to stir for 18 h. The mixture was filtered through a 0.45 μm fritted funnel and the remaining material purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (3.7 mg, 13%) as a trifluoroacetate salt. MS (ES) m/e 518.2 $[M+H]^+$.

Example 206

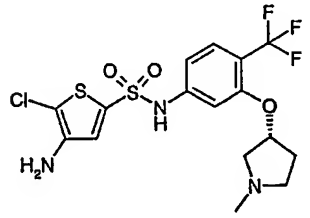
5-hydroxy-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide



A mixture of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (25 mg, 0.051 mmol), cesium carbonate (166 mg, 0.51 mmol), and 1-methyl-4-piperidinol (29 mg, 0.25 mmol) in dimethylformamide (1 mL) was heated in a Personal Chemistry microwave reactor at normal power for 900 sec at 170 °C. The mixture was filtered through a 0.45 μm fritted funnel and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to provide an unexpected 5-hydroxythiophene product (7 mg, 24%) as a trifluoroacetate salt with no incorporation of the 1-methyl-4-piperidinol group. MS (ES) m/e 468.2 $[M+H]^+$.

Example 207

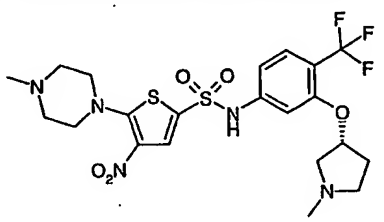
4-amino-5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide



To a solution of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (40 mg, 0.082 mmol) in tetrahydrofuran (1 mL) and aqueous sodium carbonate (1 mL of a 2 M solution) was added sodium hydrosulfite portionwise (spatula tip). The pH of the solution was monitored closely and if necessary more aqueous sodium carbonate was added to keep the solution basic (pH>8). The progress of the reaction was followed by TLC and addition of sodium hydrosulfite was discontinued once all the starting material had been consumed. The reaction was diluted with

ethyl acetate (10 mL) and water (3 mL) and the layers separated. The organic layer was washed with water (3 x 3 mL) and concentrated under reduced pressure. The remaining material was purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to provide the desired product (1 mg, 1.8%) as a trifluoroacetate salt. MS (ES) m/e 456.4 $[M+H]^+$.

Example 208 5-(4-methyl-1-piperazinyl)-*N*-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-

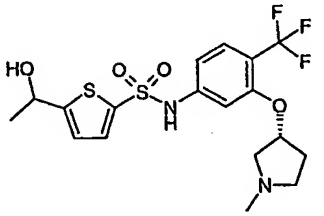


(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide

A solution of 5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4-nitro-2-thiophenesulfonamide (68 mg, 0.14 mmol) and 1-methylpiperazine (42 mg, 0.42 mmol) in dimethylformamide (1.5 mL) was heated in a Personal Chemistry microwave reactor at normal power for 600 sec at 200 °C. The mixture was filtered through a 0.45 μm fritted funnel and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (22 mg, 24%) as a trifluoroacetate salt. MS (ES) m/e 550.0 $[M+H]^+$.

Example 209

5-(1-hydroxyethyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide



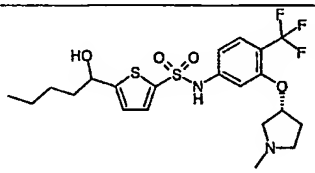
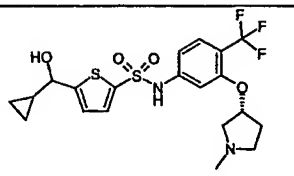
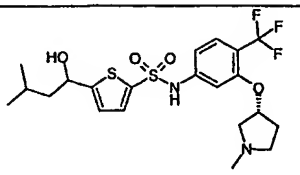
A solution of 5-bromo-2-thiophenesulfonyl chloride (0.503 g, 1.92 mmol) in methylene chloride (2 mL) was added to a solution of 3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)aniline (0.501 g, 1.92 mmol) and pyridine (0.456 g, 5.76 mmol) in methylene chloride (8 mL). The solution was maintained at room temperature for 16 h. The volatiles

were removed *in vacuo* and the remaining crude material purified by column chromatography (200 g silica gel 60, 230-400 mesh, 50% ethylacetate/hexanes-5% methanol/methylene chloride as eluent) to provide 5-bromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (565 mg, 61%). MS (ES) m/e 485.0 $[M+H]^+$.

To a solution of 5-bromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (85 mg, 0.18 mmol) in tetrahydrofuran (1 mL) at –78 °C was added *n*-BuLi (0.24 mL of a 1.6 M solution in hexanes, 0.39 mmol). After 5 min, a solution of acetaldehyde (0.1 mL, excess) in tetrahydrofuran (0.1 mL) was added. Within 10 min the reaction was quenched by the addition of methanol. The solvent was removed under reduced pressure and the remaining residue purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (52 mg, 53%) as a trifluoroacetate salt. MS (ES) m/e 451.0 $[M+H]^+$.

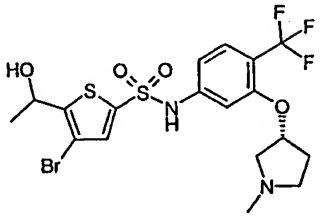
Example 210-212

The following examples were prepared according to the representative procedure in Example 209 using the appropriate aldehydes as starting material.

#	structure	name	m/z
210		5-(1-hydroxypentyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	493.0
211		5-[cyclopropyl(hydroxy)methyl]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	477.2
212		5-(1-hydroxy-3-methylbutyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	493.4

Example 213

4-bromo-5-(1-hydroxyethyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-



(trifluoromethyl)phenyl]-2-thiophenesulfonamide

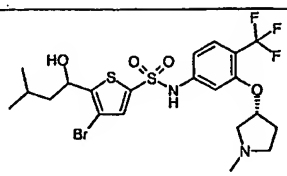
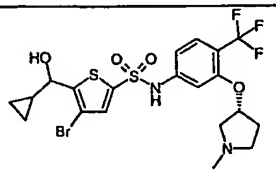
To a solution of 3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)aniline (0.50 g; 1.92 mmol) and pyridine (1 mL) in methylene chloride (5 mL) was added 4,5-dibromo-2-thiophenesulfonyl chloride (0.65 g, 1.92 mmol). The solution was maintained at room temperature for 16 h. The volatiles were removed *in vacuo* and the remaining crude material purified by column chromatography (200 g silica gel 60, 230-400 mesh, 50% ethylacetate/hexanes-2% methanol/methylene chloride as eluent) to provide 4,5-dibromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (700 mg, 60%). MS (ES) m/e 563.0 $[M+H]^+$.

To a solution of 4,5-dibromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (30 mg, 0.053 mmol) in tetrahydrofuran (3 mL) at –78 °C was added *n*-BuLi (0.20 mL of a 1.6 M solution in hexanes, 0.32 mmol). After 5 min, acetaldehyde (0.03 mL, 0.53 mmol) was added neat. Within 10 min the reaction was quenched by the addition of methanol and the solvent was removed under reduced pressure. The remaining material was dissolved in methanol (1 mL), filtered through a 0.45 μm fritted funnel, and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (5 mg, 20%) as a trifluoroacetate salt. MS (ES) m/e 529.2 $[M+H]^+$.

Examples 214-215

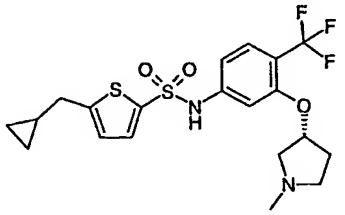
The following examples were prepared according to the representative procedure in Example 209 using the appropriate aldehydes as starting material.

#	structure	name	m/z

214		4-bromo-5-(1-hydroxy-3-methylbutyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	571.2
215		4-bromo-5-[cyclopropyl(hydroxy)methyl]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	555.0

Example 216

5-(cyclopropylmethyl)-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-

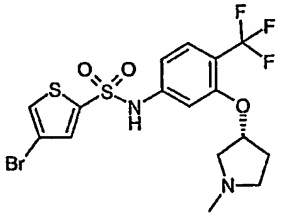


2-thiophenesulfonamide

Triethylsilane (0.5 mL) was added to a solution of 5-[cyclopropyl(hydroxy)methyl]-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (15 mg, 0.025 mmol) in trifluoroacetic acid (0.5 mL) and methylene chloride (0.2 mL). The reaction was maintained at room temperature for 16 h. The solution was concentrated under reduced pressure. The remaining crude material was dissolved in methanol (1 mL), filtered through a 0.45 μm fritted funnel, and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (8.4 mg, 57%) as a trifluoroacetate salt. MS (ES) m/e 461.2 $[M+H]^+$.

Example 217

4-bromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-

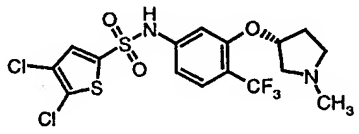


thiophenesulfonamide

A solution of 4,5-dibromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide (50 mg, 0.089 mmol) and copper (I) bromide (13 mg, 0.089 mmol) in dimethylformamide (1 mL) was heated in a Personal Chemistry microwave reactor at normal power for 300 sec at 220 °C. The mixture was filtered through a 0.45 μm fritted funnel and purified by preparative HPLC [YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile (with 0.1% trifluoroacetic acid added), B: water (with 0.1% trifluoroacetic acid added), A: 10 to 90% over 10 min, UV detection at 214 nm] to give the desired product (17 mg, 32%) as a trifluoroacetate salt. MS (ES) m/e 485.2 $[M+H]^+$.

Example 218

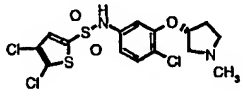
4,5-dichloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide:

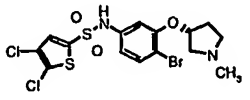
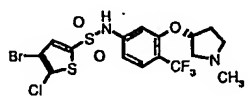
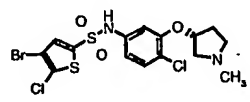
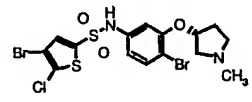
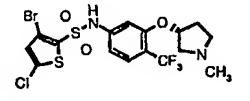
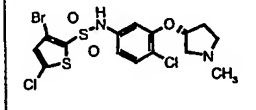
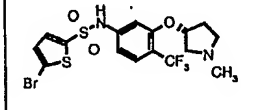
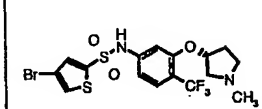
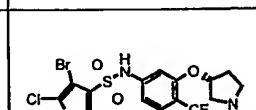


To a solution of 4-trifluoromethyl-3-((*R*)-1-methylpyrrolidin-3-yloxy)anline (2.5 g, 9.6 mmol) in acetonitrile (50 ml) and pyridine (1.5 ml) was added 4,5-dichloro-2-thiophenesulfonyl chloride (3.4 g, 13.4 mmol) at 0°C. The reaction was allowed to warm to rt and the solvent was evaporated. The residue was purified by silica gel chromatography (35 g Redisep column, silica, 40 um, 60 Å, 35 mL/min, 0-20% MeOH: CH_2Cl_2, detection at 214 nm) to give 2.80 g (62% yield) of the title compound as a light orange solid. MS (ESI) 475.0 (MH^+).

Examples 219-228

Following the general procedure in **Example 1??** except substituting 4-bromo-5-chloro-2-thiophenesulfonyl chloride, 3-bromo-5-chloro-2-thiophenesulfonyl chloride, 5-bromo-2-thiophenesulfonyl chloride, 4-bromo-2-thiophenesulfonyl chloride, or 4-bromo-2,5-dichloro-3-thiophenesulfonyl chloride for 4,5-dichloro-2-thiophenesulfonyl chloride and/or 4-chloro-3-((*R*)-1-methylpyrrolidin-3-yloxy)anline or 4-bromo-3-((*R*)-1-methylpyrrolidin-3-yloxy)anline for 4-trifluoromethyl-3-((*R*)-1-methylpyrrolidin-3-yloxy)anline the following compounds could be prepared.

#	structure	name	m/z
219		4,5-dichloro-*N*-[4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl]-2-thiophenesulfonamide	

220		4,5-dichloro-*N*-[4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl]-2-thiophenesulfonamide	
221		4-bromo-5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	
222		4-bromo-5-chloro-*N*-[4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl]-2-thiophenesulfonamide	
223		4-bromo-5-chloro-*N*-[4-bromo-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl]-2-thiophenesulfonamide	
224		3-bromo-5-chloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	
225		3-bromo-5-chloro-*N*-[4-chloro-3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}phenyl]-2-thiophenesulfonamide	
226		5-bromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	
227		4-bromo-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide	
228		4-bromo-2,5-dichloro-*N*-[3-{[(3*R*)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3-thiophenesulfonamide	

EXAMPLE 229

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Parenteral Formulation

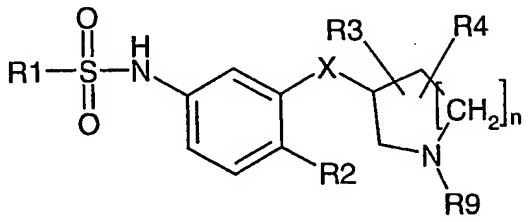
A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the

scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

R_1 is phenyl, thienyl, furanyl, pyrroyl, pyridinyl, oxazoyl, indoyl, triazinyl, imidazoyl, pyrimidinyl, oxadiazoyl, pyrazoyl, triazoyl, thiazoyl, thiadiazoyl, or pyrazinyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, OH, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl-CF_3, $O(CH_2)_qY$, NR_5R_6, $N(C_{1-6}$ alkyl)$CO(C_{1-6}$ alkyl), COR_{10}, $CONR_7R_8$, $S(O)_pC_{1-6}$ alkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$NHCOR_{11}$, or $CH(OH)C_{1-6}$ alkyl;

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3 and R_4 are independently hydrogen, C $_{1-6}$ alkyl, benzyl, $-C(R_{14})_2-OR_{12}$, $-COOR_{13}$, $-CONR_{12}$, $-C(R_{14})_2-N(R_{12})_2$;

R_5 and R_6, are independently hydrogen or C_{1-6} alkyl, or taken together form a 5-7-member saturated heterocycle optionally containing an additional heteroatom selected from N, O or S and further substituted by hydrogen, C_{1-6} alkyl, benzyl or OH;

R_7 and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl; or taken together form a 5-7-member saturated heterocycle optionally containing an additional heteroatom selected from N, O or S and further substituted by hydrogen, C_{1-6} alkyl, benzyl or OH;

R_9 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_mR_{15}$;

R_{10} is hydrogen or C_{1-6} alkyl;

R_{11} is C_{1-6} alkyl or benzyl

R_{12} is hydrogen or C $_{1-6}$ alkyl;

R_{13} is C $_{1-6}$ alkyl;

R_{14} is hydrogen or C_{1-3}alkyl;

R_{15} is phenyl, OH, or $-(C=O)C_{1-3}$alkyl;

X is O, S, or CH_2;

Y is a 5-7 member saturated heterocycle containin up to 2 heteroatoms selected from N, O or S, optionally substituted by hydrogen, C $_{1-6}$ alkyl or benzyl;

n is 0, 1 or 2;

m is 1 or 2 ;

p is 0, 1 or 2

q is 0 or 1

provided that when R_{14} is OH, m must be 2;

further provided that the compound of Formula (I) is not:

3,5-dichloro-4-hydroxy-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]benzenesulfonamide;

5-[cyclohexyl(hydroxy)methyl]-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

5-(cyclohexylmethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-thiophenesulfonamide;

N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-4-fluorobenzenesulfonamide; ;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein:

R_1 is phenyl, thienyl, furanyl, pyrroyl, pyridinyl, oxazoyl, imidazoyl, pyrimidinyl, pyrazoyl, or thiazoylsubstituted or unsubstituted by one, two, or three, of any of the following: Cl, Br, F. CF_3, OH, NO_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, $O(CH_2)_qY$, NR_5R_6, COR_{10}, $CONR_7R_8$, $S(O)_pC_{1-3}$ alkyl, CO_2H, or $CH(OH)C_{1-4}$ alkyl;

R_2 is hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl;

R_3 and R_4 are hydrogen, C_{1-3} alkyl, $-C(R_{14})_2-OR_{12}$;

R_7 and R_8 are hydrogen, C_{1-3} alkyl, or taken together form morpholine or piperidine;

R_5 and R_6 are hydrogen or C_{1-3} alkyl, or taken together form morpholine, piperidine, or pyrrolidinel;

R_9 is hydrogen, C_{1-3} alkyl;

R_{10} is hydrogen, C_{1-3} alkyl;

R_{12} is hydrogen or C $_{1-3}$ alkyl;

R_{14} is independently hydrogen or methyl;

X is O;

Y is tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperadinyl, azetidinyl all of which may be optionaly substituted by C_{1-3} alkyl;

n is 1;

p is 0, 1 or 2; and

q is 0 or 1.

3. A compound according to claim 1 chosen from the group consisting of:

N-[3-(1-methyl-2(S)-methoxycarbonylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

N-[3-(2(R)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

N-[3-(2(S)-hydroxymethyl-1-methylpyrrolidin-3(R)-yloxy)-4-trifluoromethylphenyl]-4,5-dimethoxybenzenesulfonamide;

N-[3-((R)-pyrrolidin-3-yloxy)-4-trifluoromethylphenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide.

4. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive

motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.